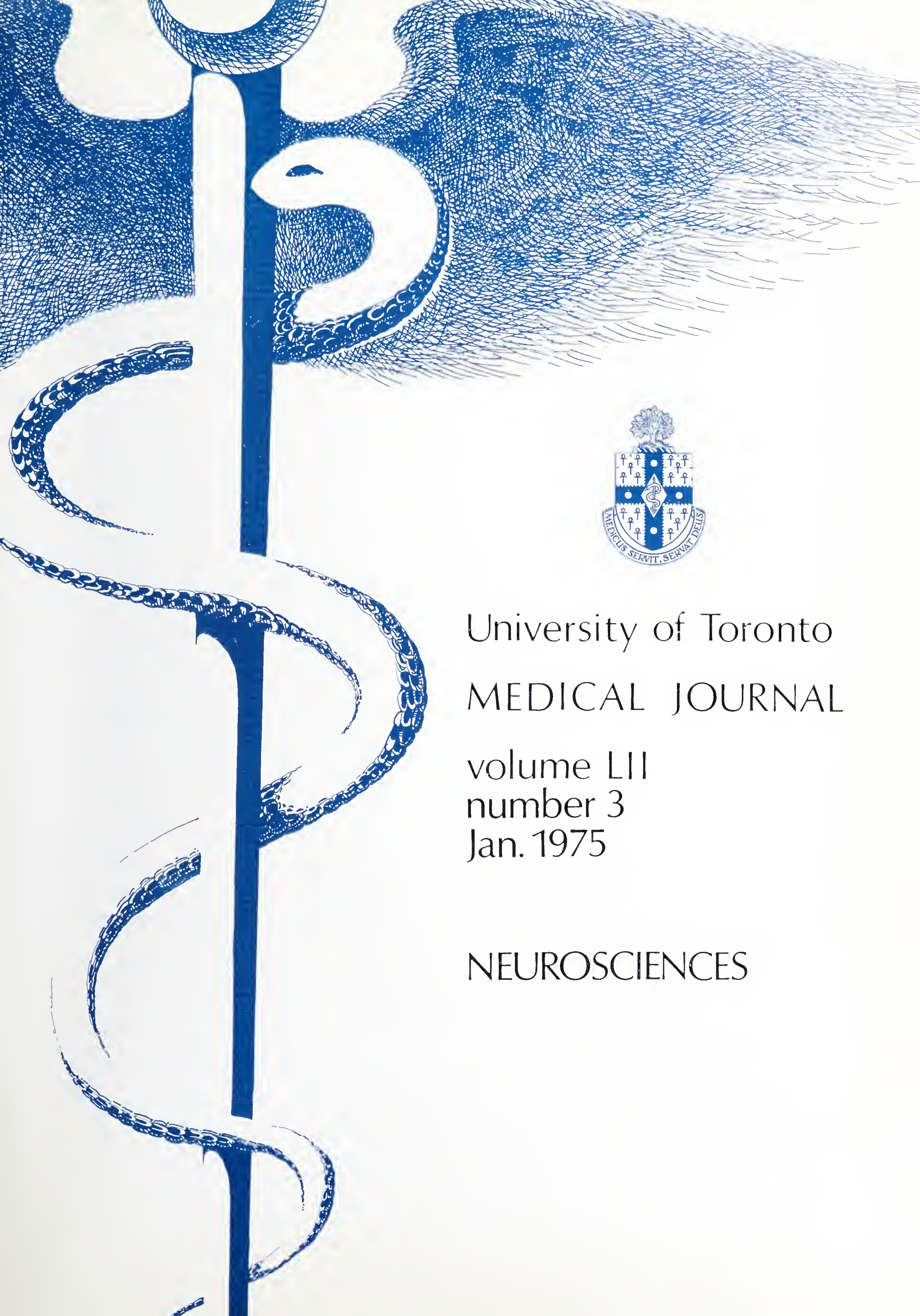


University of Toronto MEDICAL JOURNAL

volume LII
number 3
Jan. 1975

NEUROSCIENCES

the UNIVERSITY of TORONTO MEDICAL JOURNAL

Established December 1923
An Undergraduate Publication

Volume LII
Number 3
January 1975

senior editors

DAVID LAU, 7T5
MICHAEL HOWCROFT, 7T6

assistant editors

JIM FERNBACH, 7T6
BEVERLY MORNINGSTAR, 7T6
WARREN RUBENSTEIN, 7T5
HOLLI SCHLOSSER, 7T7
HARRY VINTERS, 7T6
STEPHEN WETMORE, 7T5

associate editors

NOVEMBER
WARREN RUBENSTEIN ..... *Cancer*

DECEMBER
MICHAEL HOWCROFT ..... *Ophthalmology*

JANUARY
JIM FERNBACH
HARRY VINTERS ..... *Neurosciences*

FEBRUARY
WARREN RUBENSTEIN ..... *Internal Medicine*

MARCH
..... *Therapeutics*

CONTENTS

GUEST EDITORIAL 47
Philip Seeman, M.D., Ph.D.

ORIGINAL ARTICLES

MEMBRANES DSEASES? SOME NEW IDEAS ABOUT IDIOPATHIC NEUROLOGICAL DISORDERS 49
Harry Vinters, 7T6

TRYPTOPHAN METABOLISM AND BRAIN FUNCTION 52
William H. Warren, 7T6

C.P.C.: AN UNUSUAL CASE OF DEMENTIA ASSOCIATED WITH LONG STANDING HYPERTENSION 54
James Clark Fernbach, 7T6

SPECIAL FEATURES

GRAND ROUND QUIZ 64
William Halliday, 7T5

BOOK REVIEW:

TEXTBOOK OF CHILD NEUROLOGY 65
Keith L. Meloff, M.D.

Cover Design by DAVID MacLEOD

This Journal is published five times a year from November to March, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

SUBSCRIPTION RATES: $6.00 for one volume of five consecutive issues. Single copy, $1.50.

CORRESPONDENCE should be addressed to: U. of T. Medical Journal, Room 2141, Medical Sciences Bldg., University of Toronto, Toronto 5, Canada.

Authorized as second class mail by the Post Office Department, Ottawa, and for payment of postage in cash.
Printers: Maple Leaf Press, Toronto, Ontario.

Guest Editorial

PHILIP SEEMAN, M.D., Ph.D.

Dr. Seeman is Professor of Pharmacology, Faculty of Medicine, University of Toronto. He received his B.Sc., M.Sc., and M.D. degrees from McGill University, interned at the Harper Hospital (Detroit) and received his Ph.D. working with Professor George Palade (1974 Nobel Laureate in Medicine). Dr. Seeman's teaching and research interests are in psychopharmacology and cell membranes.

Current Advances in Neuroscience and Neurology Research

Research into the nervous system is slow, frustrating, and expensive, yet its attraction and challenge are so strong that it continues to entice many medical scientists.

This issue of the University of Toronto Medical Journal contains a selection of such new findings and ideas, the full exploration of which may lead to new methods for diagnosis, prevention, and treatment of neurological diseases. For example, the clinical case report dealing with the hypertension-associated dementia raises once again the urgent question: what is the basis of dementia, and why can we not make any headway in understanding the bases and treatment of this set of diseases? One of the major difficulties in dementia research is that there is no satisfactory animal model of the disease which simulates this common and distressing human disorder. The pre-senile and senile dementias, as well as those associated with Parkinsonism, exhibit characteristic twisted neurotubules about 2000 nanometres wide, with periodic narrowings to 1000 nM every 8000 nM. The models of encephalopathy in the animals, however, wherein aluminum or spindle-inhibiting drugs or lathyrogens are used to produce the encephalopathy, do not reveal such twisted microtubules but only 1000 nM filaments. Wisniewski, Terry, and Hirano[1] have suggested that it may be necessary to look for the human analogue in such long-lived animals as parrots, elephants or the Galapagos turtle. Furthermore, the successful isolation of the dementia proteins[2] may someday lead to an accurate blood test for senile dementia.

Present knowledge of the neurophysiology and neuroanatomy of pain indicates the complexity of a topic which plays a key role in the evolution of humanity. What we do, and what we do not do, very often depends on whether it is painful or pleasurable. Yet, we are nowhere near comprehending the underlying biology! From the work of R. Burgess (U.S.A.) as well as that of B. Pomeranz (Toronto), we know that certain neurones do transmit true pain messages; but we also know from R. Melzack (Montreal) and P. Wall (England) that many other pain-carrying neurones can be modulated by sensations of touch, pressure, stroking, etc., such that pain can be turned off. Presumably this provides some biological basis for acupunctural relief of painful joints and limbs, although considerable and informed opinion exists that there is a hypnotic element involved in acupuncture. This is not to deprecate acupuncture or hypnosis, since the control of mind over matter is real (natural childbirth, it is said, can be painless and exhilarating) and the mind-body relation is now bursting with discovery with the findings of Releasing Factor substances coming from the hypothalamus, which in turn regulate endocrine and other body functions.

Claude Bernard's 'milieux intérieurs et extérieurs' are expanding every day as we learn more and more substances (foods, food additives, drugs, cigarettes, vitamins, pollutants, cosmetics, swimming pool additives, etc.) which affect our lives and the well-being of our children. It is trite to say that nothing is safe anymore. It is rather a question of dosage and the size and vulnerability of the human receiving this dosage. For example, high concentrations of orally administered and protein-building amino acids are perfectly safe in adult animals, but many can lead to at least convulsions in immature

rats. The so-called "Chinese Restaurant Syndrome" is thought to be due to excessive monosodium glutamate, an excitant neurotransmitter. Blighted potatoes are suspected in spina bifida, tea-drinking in anencephalus, cigarette-smoking in producing small babies at birth, coffee in heart disease, maraschino cherry food colouring in certain cancers, etc., – the list is endless.

In addition to glutamate, there are now thought to be about a dozen neurotransmitters in the brain, and one of these is 5-hydroxytryptamine (5-HT). Normal levels of this transmitter appear to be essential for sleep, and probably for normal mood processes, although direct proof for this latter function is still lacking. There is considerable research attempting to stimulate 5-HT synthesis in the brain.

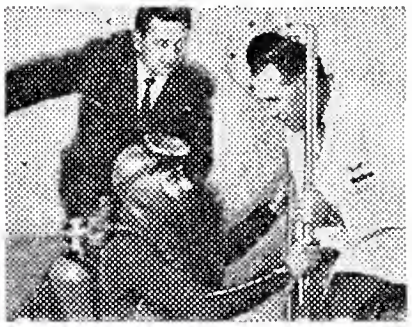
One of the current important discoveries in medicine is that of membrane receptor diseases. Membrane receptors for the neurotransmitters, as well as receptors for steroids, for convulsants and tranquilizers, and for hormones are being discovered, isolated and purified. This will open up a whole new chapter in the diagnosis of various diseases.

The ultimate goal is not only to prevent and cure disease, but to understand human behaviour as well, if this is possible. It could be, for example, that people tend to choose the right-hand staircase (or keep to the right) because the dopamine content in the contralateral striatum is slightly higher than that in the ipsilateral side; certainly this is the case in rats[3]. But human behaviour must be more complicated than this and it will probably take many hundreds of years before a clear picture of brain function emerges.

REFERENCES:

1. H. Wisniewski, R. D. Terry and A. Hirano. *J. Neuropath. Exp. Neurol. 24,* 163-176 (1970).
2. K. Iqbal, H. M. Wisniewski, M. L. Shelanski, S. Brostoff, B. H. Liwnicz and R. D. Terry. *Brain Res. 77,* 337-343 (1974).
3. B. Zimmerberg, S. D. Glick, and T. P. Jerussi. *Science 185,* 623-625 (1974).

Your years at Medical School are the hardest. So how about some help along the way?



Pre-med was tough. But med school will be tougher. So how about making things easier on yourself. How about going through the final years on the Medical Officer Training Plan (MOTP).

MOTP will help to pay your medical school expenses so you can concentrate on becoming a doctor. Instead of worrying about money problems.

MOTP will solve your summer employment by putting you to work developing military and medical skills in the Canadian Armed Forces.

When you graduate as a doctor of medicine, you're promoted to Captain. You're all set to practise your profession. At a salary equal to your professional status.

For more information contact us, your local Canadian Forces Recruiting and Selection Unit at:

25 St. Clair Ave. East
Toronto, Ontario
M4T 1M2
Telephone: 966-6564

THE CANADIAN ARMED FORCES

DRS-70-21

Membrane Diseases? Some New Ideas About Idiopathic Neurological Disorders

Harry Vinters, 7T6

Of all the juvenile onset neurological disorders, two of the most devastating are Duchenne or pseudohypertrophic type muscular dystrophy and Friedreich's ataxia. Despite their rarity and many differences, these two entities have in common a genetic basis (more clearly established in Duchenne), onset in early youth, a progressive deterioration – over years – which almost no treatment can alter, multisystem involvement, unknown etiology, and a grim prognosis. The purposes of this paper are: (1) to review the clinical pathophysiology of these two diseases and others (less severe) like them which affect many body systems; and (2) to discuss some simple experiments that have been aimed at explaining the multi-focal extent of such disorders. Both basic and clinical research findings will be considered.

The classic case of Duchenne type dystrophy is inherited as a sex-linked recessive gene, with onset early in the first decade of life. The initial complaints involve the child's locomotor difficulties due to muscle weakness, but these are often superseded by kyphoscoliosis, with cardiac and pulmonary failure. The latter are usually terminal events in the patient's early teenage years. The late cardiac pathology may manifest itself in QRS complex slurring, lengthening of the P-R interval, bundle branch blocks, and S-T segment depression or elevation. The physician is powerless to slow the disease process, although he may encourage exercise and weight control, and prescribe oral quinine to provide mild symptomatic relief. The muscle tissue pathology gives a picture of wide variation in fiber size and heavy fat and connective tissue deposition.[1]

In Friedreich's ataxia there is idiopathic spinal cord degeneration involving the posterior and lateral columns (most marked in the corticospinal and posterior spinocerebellar nerve tracts). The dorsal roots may be affected. The child with ataxic gait presents at an age between 5 and 15 years and thereafter develops hand and arm ataxia with intention tremor, dysarthria, overall weakness, nystagmus, and sometimes a profound sensory loss (postural sense and movement perception) which is most pronounced in the legs and accompanied by an absence of tendon reflexes. Aside from producing the neurological deficits, this syndrome may result in severe scoliosis, pes cavus, retinal pigmentation and/or optic atrophy, cardiac enlargement due to fibrosis and myocardial thickening, and multiple ECG changes. As in Duchenne type dystrophy, heart failure may be the ultimate cause of death, which occurs twenty years or less after the first symptoms in most cases.[2]

Two milder disorders with less widespread multisystem effects are Dystrophia myotonica and neurofibromatosis. The first of these is a form of adult onset muscular dystrophy and myotonia that causes wasting first in the face and shoulder girdle. But its traditional symptom triad includes cataracts and gonadal atrophy. Diabetes mellitus, and heart block may be present. Neurofibromatosis (von Recklinghausen's disease) has characteristic brownish skin pigmentation or café-au-lait spots, neurofibromata, and cutaneous fibromata. These are frequently accompanied by kyphoscoliosis. Aside from its disfiguring appearance, this disease may be benign unless one of the tumors becomes malignant or causes compressive symptoms in the central nervous system.[2]

In spite of their variable pathology and clinical course, all of the above diseases have in common a diffuse constellation of signs and symptoms. Ramifications of the basic abnormality (assuming such exists) appear to extend into the nervous, musculoskeletal, cardiovascular, and even integumentary systems. Tissues with excitable membranes, notably skeletal muscle and the conducting system of the heart, are especially at risk. In speaking of such broad pathologic processes, however, it seems artificial to subdivide the systemic collapse into organ systems. Recognition of this has led some investigators into the crucial studies, described below, to elucidate the site of a 'molecular' lesion that could cause such whole body degeneration.

Given the importance of the external and internal cellular membranes as (a) regulators of ionic-osmotic content, and (b) as sites of most enzymatic reactions in all cells, this was a logical place to start in the search for a defect. Most of the recent experiments in this area have been related to the dystrophies – as they are the more clinically common – in either human subjects or appropriate animal models.

Morse and Howland[3] discovered significant surface deformation (e.g. pseudopod-like protrusions) in 26.9% and 51.6% of erythrocytes from two distinct strains of mice with congenital muscular dystrophy; normal control mice from the same litters had about a 4% rate. The severity of the muscle disease paralleled the amount of distortion. Furthermore, the same red cell changes were found in dystrophic rats in which the dystrophy had been induced by a vitamin E restricted diet. In 1974, Matheson and Howland[4] showed a remarkably high proportion of structural abnormalities in saline-washed erythrocytes from Duchenne muscular dystrophy patients. Using the scanning electron microscope, as in the initial study, they found Duchenne patients to have from 20.6% to 98.4% of circulating RBC's showing visible distortion (normal range 3.2% to 7.4%). There was even some direct correlation between this percentage and the age of the affected patient. They further showed that limb-girdle and facioscapulohumeral dystrophics have a higher than normal percentage of deformed RBC's (approximately

17% to 36%). Most important, they observed erythrocytes from likely female carriers of the Duchenne trait – as suggested by strong family history and serum creatine phosphokinase elevations – and found their blood to show a 34% to 40% RBC distortion rate. They suggest that the membrane alterations result from an abnormal lipid content and speculate that this abnormality occurs in most of the patient's cells. Arguing in favour of a lipid defect is the observation that normal erythrocytes exposed to lysophosphatides and fatty acids take on a configuration like the aberrant Duchenne cells.

Whatever the biochemical disorder, Howland[5] has shown that it alters the membrane permeability to K^+. Though the steady state K^+ content of normal and Duchenne dystrophic RBC's is roughly equal, the dystrophic cells show a K^+ efflux rate five times that of healthy erythrocytes, as detected using a highly sensitive K^+ electrode. The suspended mitochondria from brains and livers of dystrophic mice exhibit an energy-dependent increase in K^+ conductance over normals, which have a very low K^+ permeability. Thus a widespread leakiness to K^+ in dystrophic muscle cells could well explain the clinical signs and symptoms of the disease, in view of the importance of K^+ and Na^+ balance across the sarcolemma in excitation-contraction coupling. As Howland points out, the K^+ shift as an etiologic factor in dystrophy may also provide a clue as to why hypokalaemic periodic paralysis is more common in affected families.

Early *in vitro* experiments established mitochondrial disease in genetically dystrophic mice.[6] The respiration rates and membrane potentials of mitochondria are significantly lower in material from dystrophic mice than in suspensions from their disease-free littermates; this, despite the same oxidation state and quantity of respiratory cytochromes present in the organelles. The primary metabolic difference is an impermeability to protons in the dystrophic mitochondria. This proton transport rate is so much lower than in normals that it explains, on thermodynamic grounds, the respiratory malfunction. The disorder results in slower movement of malonate anions into the mitochondrion, due to unfavourable proton distribution about its membranes.

In all of the above experiments, deficiencies have been shown to exist in membrane systems far removed from the sarcolemma and sarcoplasmic reticulum. The tissues studied did not have any associated gross pathology – indeed, the dystrophic livers used as a source of mitochondria[6] were normal by histologic and biochemical standards. If pathology was present, it was in a form too subtle to be detected. Or it may be that only the functional status of muscle is so delicate as to be disrupted by ionic shifts; i.e., other tissues are spared or affected just as the disease nears its end stage.

The membrane adenosine triphosphatase (ATPase) enzymes of patients and animals with muscle disorders have also been investigated.[7] The red cell ghosts and leg muscle membrane fraction from (1) white Pekin strain ducks (which often develop a severe idiopathic myopathy) and (2) normal Mallards were isolated. They were then compared with respect to baseline ATPase activity and ouabain effect on the ATPase. The baseline activity in all animals was near normal. However, the Mallard and normal Pekin membrane systems showed the expected inhibition (by 35-40%) of ATPase with ouabain, whereas the membranes from Pekin ducks judged to be myopathic (based on light microscopic tissue examination) showed a stimulation (by 23-28%) of the ATPase. In extending this study to human erythrocyte ghosts[8], the same paradoxical response to cardiac glycoside was observed in all patients with adult onset spontaneous muscular dystrophy and myotonia, though stimulation was over a wide range (15-68%). Of the eight Duchenne children's cell samples tested, five showed ATPase stimulation (by 25-77%), two showed no response to 10^{-4} molar ouabain, and one showed normal ATPase inhibition in the control range (29-82%). In the same clinical series, limb-girdle dystrophics' red cell membranes had a variable response in both directions.

These data have been verified[9] and extended by observing red cell ATPase function in (a) two mothers carrying the Duchenne trait, and (b) patients with other neurologic disorders which are thought to have a membrane component in their pathophysiology. (These included nonprogressive myopathy, post-thymectomy myasthenia gravis and MG with thymoma, thyrotoxic periodic paralysis, and paralysis agitans). In the former pair of female carriers, ATPase ouabain suppression was normal; in the latter group, activity was also reduced by about 10%. The experimenters proved that there is no consistent relationship between the level of enzyme activity in Duchenne's and patient age, disability, or serum CPK values. Therefore, the ATPase derangement seems to be unique to the dystrophies, and is especially prevalent in the Duchenne variety.

Purified sarcolemma from normal and dystrophic hamsters has been obtained[10], and its Na^+-K^+ stimulated, Mg^{++} dependent ATPase looked at. The ATPase from diseased hamsters had a much higher ATP hydrolyzing activity, in both Na^+-K^+-stimulated and Mg^{++} ATPase portions. Also, the abnormal Na^+-K^+-ATPase was much more potent for all concentrations of Na^+ and K^+ added into the incubation medium, and over a pH range of 6.8 to 7.6. Both normal and dystrophic Na^+-K^+-ATPase were suppressible with ouabain. Though some of these findings appear to be at odds with those discussed above, the difference may be due to natural species variation. In any event, it provides further rationale for seeking dystrophic membrane changes that could influence the constituent ATPase by, for example, a conformational enzyme change related to membrane components.

Even platelets from Duchenne patients have been implicated as bearing a membrane transport defect.[11] This relates to the platelet's property of taking up 5-HT (serotonin). Though there is no difference in the circulating plasma 5-HT level between dystrophics and normals, the patients have a lower platelet level of this compound (by approx. 50%). The radioisotope ^{14}C has been used to label 5-HT and by this means follow its movement into and out of platelets in plasma. In this way, it was discovered that the initial 5-HT platelet influx was diminished in dystrophics, but that the total ability to concentrate 5-HT and the rate of 5-HT loss were not affected. Ouabain in this case depressed the early 5-HT influx (another ATPase related process) uniformly in controls and dystrophics. It is of interest that one of the three control groups for this trial consisted of matched children with non-Duchenne neuromuscular problems, including one with Friedreich's ataxia and four with myotonic dystrophy. Yet the results from this control group were within normal limits. It again indicates a specific, possibly narrow membrane deficit in the Duchenne children.

Ultrastructural examination of dystrophic muscle itself has been of limited value in assessing the condition of the sarcolemma – the pathology in the muscle cell can be so great that an abnormal appearance of the membrane does not necessarily localize the prime defect there. Some of the progressive membrane changes that occur are not specific to dystrophy, but are seen in a milder form with other nerve-muscle diseases. In dystrophic hamsters, these include widening of the sarcotubular system (accentuated by the stress of prolonged exercise), intracellular edema, indicating a permeability increase and, finally, disintegration of the sarcolemma after loss of the myofilaments.[12] Of these electron microscopic alterations, severe sarcotubular widening is found in familial periodic paralysis. The advent of scanning EM has added some knowledge.[13] In biopsy specimens from dystrophic patients, SEM has detected cell surface closure of the vital T-tubular system, and loss of the A-I banding pattern. The change is not a diagnostic one since similar findings are common with muscle in which neurogenic atrophy has taken place.

Lipid studies, using thin layer chromatography of biopsied muscle extracts, have shown that the lipid pattern in Duchenne muscle is akin to that of immature muscle. This means that the profile is abnormal in its content of sphingomyelin (increased), lecithin+ choline plasmalogen (decreased), and total cholesterol (increased). But the importance of this combination for specific membrane functions is unknown.[14]

Although this article may seem more a review of some esoteric aspects of Duchenne type muscular dystrophy than a consideration of 'membrane diseases', I have chosen to emphasize that entity because it is the best characterized and one of the commonest of the fatal neuromuscular disorders of childhood. Despite its well-known clinical concomitants, little is understood about its etiology. Various theories have been proposed to explain its mechanism of action, including chiefly muscular, neural[15], autoimmune, or vascular ones. It is possible that the basic lesion, however, is a systemic membrane defect, or that a membrane mechanism is the 'final common pathway' of the pathologic process. The same may hold for the other clinical conditions discussed at the outset. If it proves to be true, definitive treatment of these disorders may still be years away; i.e., it may have to await an era of genetic engineering, when the enzymes responsible for constructing the cell membrane can be successfully manipulated. But until proof of one or another cause for these diseases is forthcoming, they will remain a therapeutic enigma.

ACKNOWLEDGEMENT

The idea for this article was the result of a discussion with Dr. D. R. Crapper, who also reviewed the manuscript.

REFERENCES

1. Adams, R. D., and Tyler, F. H. in *Harrison's Principles of Internal Medicine* edited by Wintrobe, M. W., et al, 1927-1932, McGraw-Hill Book Co. Inc., New York, 1974.
2. Bannister, R., editor, *Brain's Clinical Neurology,* 319-389, Oxford University Press, London, 1973.
3. Morse, P. F., and Howland, J. L., *Erythrocytes from animals with genetic muscular dystrophy.* Nature, *245,* 156-157, 1973.
4. Matheson, D. W., and Howland, J. L., *Erythrocyte deformation in human muscular dystrophy.* Science. *184,* 165-166, 1974.
5. Howland, J. L., *Abnormal potassium conductance associated with genetic muscular dystrophy.* Nature, *251,* 724-725, 1974.
6. Howland, J. L., and Challberg, M. D., *Altered respiration and proton permeability in liver mitochondria from genetically dystrophic mice.* Bioch. Biophys. Res. Comm., *50,* 574-580, 1973.
7. Brown, H. D., Chattopadhyay, S. K., Patel A., and Rigdon, R. H. *Glycoside effect upon membrane enzymes of erythrocytes and muscle in duck myopathy.* Experientia, *23,* 522-523, 1967.
8. Brown, H. D., Chattopadhyay, S. K., and Patel, A. B., *Erthyrocyte abnormality in human myopathy.* Science, *157,* 1577-1588, 1967.
9. Araki, S., and Mawatari, S., *Ouabain and erthyrocyte-ghost ATPase.* Arch. Neurol., *24,* 187-190, 1971.
10. Sulakhe, P. V., Fedelesova, M., McNamara, D. B., and Dhalla, N. S., *Isolation of skeletal muscle membrane fragments containing active Na^+-K^+-stimulated ATPase.* Bioch. Biophys. Res. Comm., *42,* 793-800, 1971.
11. Murphy, D. L., Mendell, J. R., and Engel, W. K., *Serotonin and platelet function in Duchenne muscular dystrophy.* Arch. Neurol., *28,* 239-242, 1973.
12. Caulfield, J. B., *Electron microscopic observations on the dystrophic hamster muscle.* Ann. N.Y. Acad. Sci., *138,* 151-159, 1966.
13. Sakuragawa, N., Sato, T., and Tsubaki, T., *Scanning EM study of skeletal muscle.* Arch. Neurol., *28,* 247-251, 1973.
14. Hughes, B. P., *Lipid changes in Duchenne muscular dystrophy.* J. of Neurol. Neurosurg. & Psych., *35,* 658-663, 1972.
15. Gallup, B., and Dubowitz, V., *Failure of "dystrophic" neurones to support functional regeneration of normal or dystrophic muscle in culture.* Nature, *243,* 287-289, 1973.

Tryptophan Metabolism and Brain Function

William H. Warren, 7T6

The metabolism of tryptophan has recently become the subject of a great deal of research. This has led to the recognition of its unique position among the amino acids.

Tryptophan is one of the essential amino acids of the body. Not only is it in limited supply, but it is in lowest concentration of all the amino acids in the liver. Thus it tends to be a limiting factor (only in liver as far as we know) in the rate of hepatic protein synthesis.

Tryptophan is also the only amino acid that binds to any appreciable degree to serum albumin, generating two functional compartments. The albumin bound compartment is physiologically inactive and comprises about 80-90% of the serum tryptophan. The remaining 10-20% non-albumin bound, or free compartment, is the factor correlating with the physiologic effects of plasma tryptophan. These two compartments are in equilibrium, allowing the albumin bound pool to act as a circulating store in times of high tryptophan utilization.

Many factors determine the degree of binding of tryptophan to serum albumin. One of the most important of these is the concentration of serum non-esterified fatty acids which selectively bind to serum albumin in competition with plasma tryptophan. Thus, in times of high plasma N.E.F.A., free tryptophan levels would rise, although the total tryptophan levels could remain constant. It is in this way that plasma free tryptophan becomes an indication of the state of body nutrition and metabolism.

The body utilizes tryptophan in several ways. As an amino acid, tryptophan is a substrate in protein synthesis. Also, tryptophan is the precursor of nicotinamide adenine dinucleotide, which is synthesized in the liver by the tryptophan pyrrolase pathway. In addition, tryptophan is the precursor of 5-hydroxytryptamine (serotonin), which has been shown to be synthesized in mast cells, chromaffin cells of the intestinal mucosa, and in brain tissue. It is the latter that is the subject of this paper.

Plasma serotonin does not appreciably cross the blood-brain barrier. Rather, the plasma free tryptophan is actively transported into the brain cell, and converted to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase. This is the rate limiting step in serotonin synthesis. However, this enzyme is not saturated with tryptophan substrate, and so the concentration of available tryptophan becomes the rate limiting factor. 5-HTP is converted to 5-hydroxytryptamine (serotonin) by 5-HTP decarboxylase. Serotonin is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) which can be measured in the cerebral spinal fluid and the urine.

Recent evidence suggests that serotonin could be a central neurotransmitter, playing an important role in several aspects of behaviour, thermoregulation, pain sensitivity, and central influence on the pituitary-adrenal axis.

The rate of metabolism of tryptophan has been found to vary markedly in different brain areas. 5-HT synthesis is most pronounced in the hypothalamus, the corpus striatum, and the median raphe nuclei in the dorsal midbrain. There is very little synthesis in the cerebral cortex, spinal cord, and thalamus, and almost no activity in the cerebellum. The rate of serotonin turnover in the different areas of the brain shows the same pattern of distribution. Presumably, this reflects the selective use of 5-HT in neurotransmission.

One of the most promising areas of research of tryptophan and behaviour function, has been in the field of sleep regulation. The rate of synthesis of 5-HT in the median raphe nuclei could very well be important in this respect. These nuclei are located near the mesencephalic reticular formation. It has long been known that a lesion in this area will produce subtotal insomnia for at least two weeks. One of the most popular theories is that the onset of sleep begins by triggering the 5-HT sleep system. There is evidence that 5-HT triggers slow wave sleep (SWS). The inhibition of 5-HT synthesis pharmacologically with PCPA (Parachlorophenylalanine) leads to insomnia which is reversed by the administration of 5-HTP. Lesions in other areas of the brain which lead to hypersomnia have been associated with an increase in 5-HT turnover.

Others have investigated the possibility that 5-HT is important in thermoregulatory control. Microinjections of 5-HT in the preoptic area of the anterior hypothalamus provoke hyperthermia. It has also been shown that peripheral cooling evokes up to a 24-fold increase in the release of 5-HT in this area. The current view is that 5-HT release in the rostral part of the hypothalamus promotes heat production, but this is in balance with norepinephrine, which antagonizes this action. This is the monoamine theory of thermoregulation proposed by Feldberg and Myers.

There has been evidence that serotonin is important in pain sensitivity. In rats, it has been proposed that 5-HT acts to inhibit the effects of a painful stimulus. The 'jump threshold', used as a measure of pain sensitivity, is directly proportional to the telencephalic content of 5-HT. Inhibition of serotonin synthesis has been shown to lower such a pain threshold. However, when serotonin synthesis is stimulated pharmacologically, no degree of analgesia can be demonstrated.

Drugs that alter brain 5-HT content have been shown to alter pituitary-adrenal function. Drugs inhibiting the synthesis of 5-HT increased plasma corticosteroids and reduced the degree of diurnal variation. There was enhanced and prolonged secretion of ACTH in response

to stress. Increasing the brain 5-HT has been shown to reduce this stress response. These results suggest that brain serotonin may be the mediator of a negative feedback mechanism regulating pituitary-adrenal function. The site of this action is possibly at the hypothalamus, which regulates the pituitary secretion of ACTH by a releasing factor.

The possibility that brain serotonin plays a role in male sexual behaviour is clearly indicated by some animal experiments. There have been several reports that pharmacological depletion of brain serotonin in rats increased copulatory frequency and decreased ejaculatory latency. Some workers have found similar behaviour among rabbits. Such reports have led to speculation that PCPA is an aphrodisiac, as reported in PLAYBOY Vol. 17, p. 54 (April, 1974). However, in subsequent studies with rhesus monkeys, no changes in sexual behaviour or dominance patterns could be observed.

In man, PCPA has been used in the treatment of carcinoid syndrome, where there is increased synthesis of serotonin by the intestinal mucosa. Such investigations were conducted under double blind conditions. A number of behavioural changes occurred, including depression, restlessness, and anxiety. However, neither thought content, nor self-rated sex interest, changed during the treatment. Similar findings have now been reported in PCPA treatment of normal male volunteers.

There has been a great deal of research conducted on the biogenic amine hypothesis of affective disorders. This hypothesis is based on the theory that emotional disorders such as depression, can be the direct behavioural disturbance of an abnormality in the biogenic amines in the brain. These studies have, by the very nature of the disturbance, been limited to human subjects, by subjective estimations and by CSF determinations of metabolites.

There are two main groups of evidence for the biogenic amine hypothesis of depression. One of these is the observation that pharmacologic procedures that decrease amines in the brain induce depression in mentally normal subjects. Furthermore, procedures that elevate amines in the brain – antidepressants and precursors of the amines, such as tryptophan, alleviate depression.

The other evidence arises from the direct biochemical investigation of patients suffering from affective disorders.

Two drugs that decrease biogenic amines in the brain are reserpine and PCPA, (already noted to induce depression in experiments on sexuality). The action of the commonly used antidepressant drugs is to increase the amount of free amines present, either by decreasing their metabolism (monoamine oxidase inhibitors), or increasing the properties of the free amines present by interfering with cellular binding (tricyclic antidepressants). Since these two drug groups increase both catecholamines and serotonin, attempts have been made to determine the relative importance of these two transmitters. It has been found that depressed patients maintained on MAO inhibitors and supplementary tryptophan, recovered very significantly better than those on MAO inhibitors and a placebo. A comparable effect has not been shown with MAO inhibitors and L-DOPA, a precursor of the catecholamines. The brain levels of 5-HT and 5-HIAA have been shown to be lower in suicides than when compared with a control group of autopsy specimens. However, in experimental subjects, the samples have to be limited to lumbar CSF taps.

Since catecholamines and serotonin cannot be detected in the CSF, the acid metabolites of these amines must be followed. These are homovanillic acid (HVA) and 5-HIAA respectively. Many factors influence this assay and the results are difficult to interpret.

As early as 1966, a decreased concentration of these acid metabolites was reported in the CSF of depressed patients. Several reports have confirmed this finding. This constitutes one of the major pieces of evidence for the 5-HT depletion theory of depressive illness.

It is important to note, however, that after the patient was clinically well, and free of drug therapy, the low levels of CSF 5-HIAA persisted. This suggests that clinical recovery is not accompanied by any change in this abnormality, and therefore it is probably a predisposition that requires other factors to produce the clinical picture. However, measures to increase 5-HT by MAO inhibitors and large doses of tryptophan can be a very effective treatment of endogenous depression. It is thought that the change in amines has a direct relationship to some of the symptoms of depression.

For many years, electroconvulsive therapy has been used, with considerable success, in the treatment of depression. In 1972, evidence was published that ECT to normal rats stimulated serotonin synthesis in the brain. ECT was shown to increase brain serotonin and 5-HIAA concentration. This effect was best seen only 30 minutes after a single treatment. The proposed mechanism of this action is a stimulation of transport of tryptophan into the brain cells. This has raised the possibility that this could be related to the therapeutic effects of ECT.

The efficacy of lithium salts in the treatment of endogenous depression has also been well documented. In 1971, evidence was published that, in rats, lithium increased the concentration of 5-HT and HIAA secondary to increased 5-HT synthesis. This increase was in the order of 80% when proportional to the human therapeutic dose. The suggestion that lithium acted

(cont. on page 6[illegible])

C. P. C.: An Unusual Case of Dementia Associated with Long Standing Hypertension

James Clark Fernbach, 7T6

CASE PRESENTATION

The exact time of onset of symptoms in this patient is difficult to ascertain. Good health existed until his early twenties, roughly twenty years before death, at which time he had completed a year of army training and was resuming his university studies. About this time he experienced several transitory episodes of blindness which occurred while he was walking and lasted ten to twenty seconds. He would stop walking, pretend to be doing something with his hands, and his vision would return quickly. On several occasions there was diplopia with horizontal splitting of the images. The patient was a proficient and enthusiastic athlete, but after his military experience his zest for exercise diminished and he would become easily weakened and fatigued.

Despite these transient episodes, he was a superior student and completed B.A. and M.A. in commerce. A physical examination for insurance purposes in 1956 showed him to be hypertensive. He complained at this time of giddiness and right anterior chest soreness, and a diagnosis of "emotional" hypertension was made. He was refused life insurance and further advancement in his company.

A history of the blood pressure was obtained from his family physician. When he was first seen in 1949 his B.P. was 120/80. In 1951 he presented complaining of "dizziness" of two months' duration and right sided headache. His B.P. was 160/90. In addition, he complained of redness and flushing of his face. This, along with a livid blotchiness which would be especially exaggerated on his trunk and thighs after exercise, had been present intermittently since adolescence. In 1953 his B.P. was 150/90; in 1955 it was 170/90. In 1957 the B.P. was 240/100, and in 1959, 210/110.

Once during this period, when completing his M.A. degree, he awoke in the morning with a left sided hemiparesis which improved slowly, leaving him weak on his left side for sometime thereafter. Throughout the interval 1946 to 1959 incidents of transitory blindness would recur, but apparently increased in frequency at the time of the hemiparesis. Also, he began to experience mild transitory ataxia and increasingly severe vertigo. By 1961 these symptoms had progressed to generalized incoordination and clumsiness; dysarthria then appeared and was followed by decreasing ability to concentrate.

In 1959 investigation of the hypertension was carried out at St. Michael's Hospital. Chest x-ray showed slight enlargement of the left ventricle, B.U.N. was normal and albumin showed as a trace in the urine. Aortogram showed normal renal vessels. A double collecting system was demonstrated, with two ureters meeting at L2,3 and a single ureter entering the bladder on the right. Urine culture showed no growth, and I.V.P. was normal. A differential Na^+ excretion test showed equal volume and Na^+ excretion from both kidneys, with an acid urine. A diagnosis of essential hypertension was made, while no dysfunction of the nervous system could be demonstrated. He was not treated at this time.

In 1961 the patient was in New York City, working for a Ph.D. in finance. His previously described neurological symptoms prompted him to seek medical care, and he was seen by several private physicians in that city. They treated his hypertension with Serpasil, Hygroton and guanethidine, but adequate control was not achieved. In 1962 he was hospitalized in Mt. Sinai Hospital in New York where a diagnosis of peripheral vascular disease with dementia was made. Electrolytes were normal, aside from a K^+ of 3.6 meq./1. This may have been attributable to recent diuretic therapy. Muscle and skin biopsies were normal as was his E.S.R. His eosinophile count was elevated above normal on one determination, but this was not repeated. A lumbar puncture showed an opening pressure of 60 cm. H_20 with sugar and protein levels of 29 mg. % and 25 mg. % respectively. Serology and colloidal gold tests were negative. I.V.P. was normal and B.P. was 140/110. Ischaemia of the left great toe was present. It was red and tender with a black portion near the tip of the nail. The peripheral pulses were all present and normal.

Neurological examination revealed slight left ptosis and bilateral past pointing, with poor performance of rapidly alternating movements (dysdiadochokinesia). At this time the patient lost his ability to coordinate fine movements necessary for writing and had to hire a secretary to write for him. For a period he became dysarthric to the point of being incoherent.

In July 1962, he was admitted to Toronto Western Hospital, where a C.N.S. examination was reported as normal. There was a low pitched grade I early diastolic murmur over the pulmonic area. The left great toe was purple, and the skin there atrophic. There was marked generalized livido reticularis; serum K^+ was 3.8 meq./1. An elective left sympathectomy was successful in relieving the ischaemia of the toe.

By the end of 1962 he could not continue his academic work. He attempted his Ph.D. examinations and failed. Returning to Toronto, he was admitted to Sunnybrook Hospital in January, 1963. An extensive investigation was carried out, including B.U.N., serology, complete hematology, electrolytes, Ca^{++}

and phosphate, skull x-ray, chest x-ray, E.C.G. V.M.A., I.V.P., aortogram, air study, neurological assessment and psychological testing. At the time, these examinations were thought to show only mild albuminuria with same granular casts, a normally excreting bifid right kidney and pelvis, normal aortogram and nephrogram and hypertension without cardiomegaly. Neurological and psychological examination revealed dementia, spastic facies and pyramidal tract disturbances with incoordination. The consensus was that this clinical picture was secondary to the patient's long standing hypertension and most likely due to multiple deep basal infarctions ("état lacunaire") in the distribution of the penetrating branches of the anterior and middle cerebral arteries.

In 1964 progressive deterioration prompted the patient's admission to the Wellesley Hospital for further investigation. He now demonstrated marked bilateral arcus senilis, bilateral nystagmus and Grade II arteriosclerotic and hypertensive changes in the fundi. There was generalized livido reticularis, a Grade I aortic and left parasternal systolic murmur which increased in intensity with exercise, and a barely audible diastolic murmur (the timing was uncertain) at the left parasternal border. The B.P. range was 210-180/140-130.

Neurological examination revealed slow mentation, dysarthria, right homonymous field defect, right facial palsy of the central type, bilateral ptosis, weakness of the orbiculares oculae, increased tendon jerks in the right arm, bilateral flexor plantar responses, increased tone and "cog wheeling" at the elbows, and bilateral impairment of cortical stereognosis. E.M.G. examination was normal. Psychological testing disclosed a verbal I.Q. of 98 with a performance I.Q. of 61. The possibility of an extrapyramidal disorder, e.g. Wilson's Disease, was suggested.

Hematological and electrolyte values were within normal limits except for a serum K^+ of 3.2 meq./1. Serum cholesterol was 235 mg. % and total lipids were 271 mg. %. Recommendation that the serum copper and angiotensin levels be measured was made, but these investigations were not carried out on this admission.

In November, 1964, the patient was admitted to Toronto General Hospital because of increasing deterioration. He was able to substantiate his previous record of investigations but was not fully aware of the severity of his condition. He admitted having had in the preceding few months several periods of absolute expressive aphasia – not being able to say what he wanted to. He denied specifically having headaches, polydipsia, polyuria, dry mouth, muscle cramps or fatigue, although he would experience vertigo with abrupt changes of posture. There was cyanosis of the right middle finger which was similar to that of his left great toe.

Investigations for Wilson's Disease were carried out, and his urinary copper excretion, serum copper and serum ceruloplasmin levels were normal. Serum K^+ at this time was consistently low, and aldosterone secretion was elevated. Aldactone A studies produced a mild natriuresis and elevation of serum K^+ to 4.5 meq./1., but there was no decrease in blood pressure (230/110 on admission). On one occasion there was 2+ albuminuria, but this was not repeated. Sugar and ketones were absent, as were cells and casts. V.M.A. was normal on two occasions. Serum uric acid, cholesterol and 2 hour p.c. blood sugar were normal. There were no cryoglobulins detected in serum after forty-eight hours and serum protein electrophoresis showed a normal protein pattern. Coagulation studies were done, both during and after heparin administration. During administration, the study was normal, but post heparin there was a prolongation of silicone clotting time with reduced prothrombin consumption. There may have been a plasma clotting defect on heparin. The E.E.G. record was disorganized, with maximum irregularity over the left hemisphere.

Before discharge, the patient was presented at neurology rounds, and the consensus was that he was suffering from "chronic hypertensive encephalopathy", even though this is a rare and infrequently made diagnosis.

In January of 1965 he was readmitted. The neurological examination was basically unchanged, showing the same signs as had been observed previously. Various investigations of the renin-angiotensin-aldosterone axis were performed and elevated plasma aldosterone, elevated aldosterone secretion rate and an elevated plasma renin level were found. A split function study showed bilaterally equal Na^+, water and creatinine excretion.

The earlier air study and aortogram were reviewed. The biventricular diameter in the brow up position actually was 68mm., in gross excess of a normal of of 42 mm. The other ventricular dimensions were correspondingly increased. As well, it was noted that the left kidney was 1.5 mm. smaller than the right, a reversal of the usual situation. Peripheral renal vessels were poorly visualized, suggesting parenchymal disease.

Although primary hyperaldosteronism was probably not as likely a cause of the persistent hypertension as was small vessel disease (elevated renin), the patient's worsening plight was felt to justify a search for a functioning adrenal adenoma, removal of which would help to control the hypertension and, hopefully, the neurological deterioration. Left adrenalectomy was performed. The gland was essentially normal, with no evidence of hyperplasia or neoplastic change. Renal biopsy, performed at the same time, showed foci of ischaemic atrophy. There were several hyalinized glomeruli, many arterioles showed hyaline arteriosclerosis and several showed hyperplasia of the arteriolar

wall. The lumina of the arteries were reduced as a result of intimal hyalinization.

The patient was discharged to Riverdale Hospital with diagnosis of cerebral atrophy, dementia, diffuse nephrosclerosis with severe hyaline and hyperplastic changes, renin elevation and secondary hyperaldosteronism and hypertension.

In November of the same year he complained of severe headache and left sided weakness. Mental deterioration without loss of consciousness ensued and he died four days later with his weakness turning into frank hemiplegia. The age at death was 42 years.

DIFFERENTIAL DIAGNOSIS

This patient presents a bewildering array of aetiological permutations. There is a long history of hypertension associated early with hypokalemia, a progressive dementia associated with repeated focal incidents, increasing motor deficits, incoordination and loss of discriminative sensory modalities, and a diffuse distal limb ischaemia, probably present since adolescence and becoming worse with age.

These conditions seem at first glance to suggest their own interrelationship, but it is necessary to consider that there may not be a single ultimate explanation for the syndrome. Questions we might ask are: 1. Was this patient's hypertension essential or was it secondary; is it not possible that it was initially the former and with time and target organ damage that it became also the latter? 2. Were the patient's dementia and neurological deterioration due to a primary C.N.S. disease, or were they vascular in origin?

One may recall, here, that wide hypertensive pulse pressures are frequently associated with arteriosclerosis, hyperthyroidism, aortic insufficiency and increased sympathetic tone, and that narrow pulse pressures are often the result of renal parenchymal disease causing an increase in both systolic and diastolic pressures. The tendency in this case for pulse pressure to initially increase with time may be significant with respect to suggesting which investigative routes were appropriate, but the increase in both systolic and diastolic pressures prior to the first work up in 1959 reduces the value of this parameter alone. As the pattern of hypertension did not conform to a recognizable syndrome, it was necessary to think in broad terms, and investigations for renovascular, renal parenchymal and endocrine causes were carried out over the years.

Renovascular disorder was ruled out in 1959 by means of aortogram. At that time the renal arteries were shown to be normal, and split function tests were normal. By 1965 there was no demonstrable functional change in the renal arteries, and there was bilaterally equal excretion of salt and water.

Renal parenchymal disease suggested itself in several ways throughout the history. Elevated blood pressure does not usually occur early in this condition; the degree of damage is quite severe before hypertension sets in. Therefore, it is a matter of interest whether the kidney damage preceded the hypertension or vice-versa and whether the hypertension was a cause or an effect of the apparent renal involvement. Common diseases that must be ruled out are pyelonephritis, glomerulonephritis, collagen disorders, (especially polyarteritis nodosa), Kimmelstiel-Wilson glomerulosclerosis, polycystic disease and kidney disease due to hyperuricemia.

Glomerulo-tubular imbalance and salt and water retention can be caused by disease affecting the glomeruli or renal arterioles and arteries, leaving the tubules intact, or conversely the tubules may be the site of damage.

Pyelonephritis, without extension to glomeruli, initially would prevent salt retention, but the course of events in this disease latterly involves the glomeruli, and the net result is often salt retention. Since there was never any demonstrated urinary obstruction or reflux, pyelonephritis is unlikely to have been a factor in the ultimate damage to the kidneys.

Glomerulonephritis, polyarteritis, intercapillary sclerosis and glomerulosclerosis would all cause relatively greater tubular resorbtion of salt and, hence, a tendency to elevated blood pressure.

Polyarteritis was considered in 1962 because of an elevated eosinophile count. Muscle and skin biopsies, however, were normal and there was no evidence of this disease afterwards; the elevated eosinophile count was never repeated.

Renal biopsy in 1965 showed hyaline arteriosclerosis, and the plasma renin at that time was above normal. It is likely that these changes were secondary, and served to complicate an existing lesion. No glomerulonephritis, either chronic or acute, was present, and there was no indication of infection being related temporarily to blood pressure. The absence of diabetes excludes Kimmelstiel-Wilson nephropathy, and that of gout and hyperuricemia induced obstruction of the renal papillae by urate deposition. Repeated x-ray studies clearly ruled out the possibility of polycystic disease.

Endocrinopathies to be ruled out are disorders of thyroid and adrenal secretion. Hyperaldosteronism was suggested early when it was first noticed that the serum K^+ was consistently low. Primary hypersecretion was definitely excluded by adrenalectomy and the failure to find a secreting tumour or any hyperplasia of the gland. However, secondary hyperaldosteronism was proven in 1965 by the demonstration of elevated plasma renin and by measurements of high plasma levels of aldosterone.

Pheochromocytoma was excluded by repeatedly normal V.M.A. determinations. A phentolamine blocking

test was performed on the last admission and this also was within normal limits.

Thyrotoxicosis and myxoedema would cause isolated increases in systolic and diastolic pressures, respectively. As there were no signs or symptoms suggestive of these conditions, investigation was not thought warranted and they were dismissed as possible aetiological factors.

To summarize, this patient probably had essential hypertension which was not treated successfully and which progressed to the point of damaging small renal vessels, causing a secondary hyperaldosteronism.

In addressing the problem of the patient's neurological deterioration, one must decide whether this was a primary C.N.S. degeneration or a result of some other type of disease.

The term "dementia" has been loosely applied in the past; at this point it is appropriate to give it definition. Adams and Victor[1] regard it as a chronic process comprised of loss of cognitive function, including memory, due to degenerative disease of the brain. This is a syndrome of multiple aetiologies and various pathophysiologic mechanisms and represents a final common pathway of certain C.N.S. diseases, just as a cirrhotic liver or granular kidney can represent the end stage of many different processes. Dementia is irreversible and incurable by definition and stands in contradistinction to acute delirium states which can be reversed.

The clinical presentation of dementia is insidious, first marked by failing cognitive function, later by changes in personality, with lack of insight and judgment and, finally, there is incoherence, irrationality, mutism, slowing, aphasia, dyspraxia and loss of sensory discrimination, motor control and continuance. It should be emphasized that this condition usually does not present early with focal signs or with motor disturbances.

The classification of dementing conditions is usually made on the basis of aetiology and pathology, but for the purpose of diagnosing this patient it is most advantageous to apply a scheme which relates the neurologic findings to associated laboratory and clinical signs of other medical conditions.

Classification[2]

I. Diseases in which dementia is usually associated with clinical and laboratory signs of other disease.

- A. Hypothyroidism.
- B. Cushing's disease.
- C. Nutritional deficiencies, e.g., pellagra, Wernicke's and Korsakoff's syndromes, pernicious anaemia.
- D. Neurosyphilis: G.P.I. and meningovascular.
- E. Wilson's Disease (Hepatolenticular degeneration).
- F. Cerebral arteriosclerosis (coronary disease, pseudobulbar symptoms).
- G. Bromism.

II. Diseases in which dementia is associated with other neurologic signs but not with other obvious medical disease.

A. Invariable association:

1. Huntington's Chorea.
2. Schilder's Disease and related demyelinating diseases (spastic weakness, pseudobulbar palsy, blindness, deafness).
3. Amaurotic family idiocy and other lipidoses (myoclonic seizures, cerebellar ataxia).
4. Myoclonic epilepsy (diffuse myoclonus, generalized seizures, cerebellar ataxia).
5. Jakob Creutzfeldt disease (diffuse myoclonus).
6. Cerebrocerebellar degeneration (cerebellar ataxia).
7. Cerebral-basal ganglia degeneration (apraxia and rigidity).
8. Dementia with spastic paraplegia (spastic legs).

B. Frequent Association:

1. Cerebral arteriosclerosis.
2. Brain tumour.
3. Brain trauma – cerebral contusion, midbrain hemorrhage, chronic subdural hematoma.

III. Diseases in which dementia is usually the only evidence of neurologic or medical disease.

- A. Alzheimer's Disease and senile dementia.
- B. Pick's Disease.
- C. Marchiafava-Bignami Disease (sometimes with frontal lobe signs).
- D. Certain tumours of the frontal lobes and corpus callosum.
- E. Low-pressure hydrocephalus.

To briefly review the course of this patient's deterioration: there were early transient blind episodes and a hemiparesis which cleared rather slowly. Four years before death, episodes of dizziness, weakness and incoordination increased in frequency and severity. Writing difficulty and dysarthria appeared and ability to concentrate diminished. There was ptosis and dysdiadochokinesia. Two years before death, psychological testing revealed a decrease in intellectual ability. One year before death and thereafter, neurological examination showed slow mentation, dysarthria, slight homonymous field defect, right (central) facial palsy, bilateral ptosis, weakness of orbiculares oculae, increased reflexes in the right arm, bilateral flexor

plantar responses, increased tone and "cog wheeling" at the elbows and bilateral cortical astereognosis.

Considering the categories above, it becomes clear that this dementia can be defined as one associated with other neurological signs and signs of "non-neurological" disease. Endocrine and nutritional dificiency disorders can be excluded, as there was never any clinical or laboratory evidence adduced in support of such a diagnosis. Likewise, neurosyphilis was excluded by the relevant laboratory tests, as was Wilson's Disease. Of this group the vascular category remains tenable.

Of the second group diseases – those in which dementia may or may not be associated with other neurological signs – the vascular category is again one which cannot be excluded. Huntington's chorea, various lipidoses and Jakob Creutzfeldt Disease can be ruled out because of the absence of characteristic signs such as choreo-athetosis and myoclonus. A demyelinating lesion such as Schilder's Disease (diffuse cerebral sclerosis) or multiple sclerosis was once suggested, but the age and subsequent progressive, non-remitting course probably excludes these diseases alone.

Brain tumours and chronic subdural hematoma were ruled out by radiography and the absence of physical signs of a mass lesion and increasing intracranial pressure. Although the solitary occurrence of dementia of the Alzheimer type is ruled out by the concurrent presence of atypical physical signs, the only way to have made a definitive diagnosis in this regard would have been brain biopsy, which was not thought warranted. In sum, considerable atrophy of the cortex was demonstrated by pneumoencephalogram, and primary dementias and those which might occur in association with, or as a consequence of vascular disease, could not be ruled out.

Dementia with cerebral atrophy of vascular origin is due to multiple small infarctions.[3] A review of the pathogenesis and clinical picture of the stroke syndrome is presented below with the object of clarifying the diagnosis in this case.

Ischaemia with tissue damage is the "common denominator" of all cerebrovascular diseases.[4] In understanding its pathogenesis it is useful to bear in mind four basic notions:[5] 1. the topographic distribution of the four large arteries supplying the brain, both extracranially and intracranially, and their collateral anastomoses (extra-cranial, circle of Willis, meningeal anastomoses of Heubner, arachnoidal circles of Schmidt and Pfeiffer's capillary transverse anastomoses); 2. The idea of the hemodynamic vulnerability of the watershed areas in the junction of two great circulations or the end zone of a single circulation; 3 the total (thrombosis, embolism, vasospasm) or partial (stenosis) obstruction of afferent blood vessels; 4. The significance of a minimum blood pressure for adequate cerebral circulation.

A stroke can occur as a transient ischaemic attack (T.I.A.), as an evolving stroke, or as a completed stroke. The first of these, as its name implies, is a brief episode of neurological dysfunction with recovery, but with a proclivity for repetition. The evolving stroke is usually mild in onset, but tends to progress, sometimes to completion, leaving the patient with a residual deficit. The early episodes of blindness experienced by the patient typify the T.I.A. and his early hemiparesis is a good example of a fairly severe type of stroke in evolution. Had it not cleared, it could have been called a completed stroke.

When strokes recur in a given patient, causing multiple infarctions, there can be several clinico pathological patterns.[6] In one, there is a steadily increasing deficit which progresses over the course of weeks or months. There is deterioration of judgment, personality changes, amnesia for recent events and disregard for social conventions. Pathologically, the collateral circulation is defective, and multiple infarcts of white and grey matter are seen. In another pattern a series of small and/or large completed strokes causes pseudobulbar palsy, spastic weakness and dementia. Judgment and insight are relatively unimpaired until late, and a reactive depression may occur which increases isolation and withdrawal. This pattern is characteristically associated with widespread cerebrovascular disease and hypertension, and there are usually multiple infarctions in the territories of the penetrating vessels of the basal areas of the brain – the classically described "état lacunaire".[7] The cortex is spared.[8] A similar clinical picture sometimes evolves in a normotensive patient. There is a history of small strokes leading to drowsiness, pseudobulbar palsy and dementia. However, the site of damage here is usually cortex, with widespread scarring being common. This is probably due to failure of anastomotic circulation secondary to atheromatous blockage of large extra and intracranial vessels.[9]

In light of this patient's pseudobulbar signs, dementia, and hypertension, the early diagnosis of multiple "lacunar" infarction was not unreasonable.

The pathogenesis of cerebral thrombosis and embolism will now be considered in their relation to this case, as they are the most common causes of stroke.

The differential diagnosis of cerebral thrombosis is presented by Adams and Fisher[10] in complete form. Of the various causes which might be implicated in this case, and which have not been absolutely excluded, we should especially note atherosclerosis, collagen vasculitides and certain hematologic disorders.

Hypertension aggravates atherosclerosis and hastens

its course in cerebral vessels as in other vessels. The precise nature of this relationship is as yet a controversial matter, but it is known that there is a pronounced tendency for atheroma to be deposited in small vessels (less than 1 mm) penetrating the basal ganglia and brainstem. Although such a process could explain some of the findings in this patient, there is no clinical evidence of severe atheroma anywhere else (e.g. coronary disease) or any suggestion of an abnormal metabolic tendency to this disorder.

Polyarteritis nodosa, lupus erythematosus, rheumatoid arthritis and other, rarer, rheumatic diseases can be causative factors in thrombotic infarction. As discussed above, such diseases must be discounted here on the basis of the clinical picture, but certain fundamental tests to specifically exclude these entities were not performed, e.g., L.E. cell preparation and rheumatoid factor assay.

Hematological conditions that have been shown to cause thrombosis commonly are polycythemia, cryoglobulinemia and thrombotic thrombocytopenic purpura. The neurological picture in these diseases is that which would be caused by multiple small infarctions in various areas of the brain, and it would not be unexpected to witness a dementia in such a case. However, there is no clinical evidence of such a disease in this patient; his hematological studies were all essentially normal.

Torvik et al[11] have reported progressive dementia caused by a rare type of generalized small vessel thrombosis. In three patients with this syndrome there was no sign of primary vascular disease, and a detailed hematologic study of one showed only increased platelet consumption (probably due to continuous thrombus formation). The onset of this disease was late in life, rather than early, but it demonstrates the principle that thrombus formation may occur with no presently available explanation and cause a progressive dementia similar to that being considered here.

Cerebral embolism causes total or subtotal obstruction of large and small vessels, and the clinical presentation is a function of the size and ultimate destination of the embolus as well as its composition. Characteristically, an embolic stroke is distinguished from thrombosis by its shorter time course. Nearly half of the patients have their syndrome developed in sixty minutes or less.[12] This is a very gross way of distinguishing the underlying process in cerebral infarction; indeed, Fisher and Pearlman[13] have observed many patients with proved emboli in whom the rate of onset of symptoms was slow. They report cases of evolving strokes, premonitory T.I.A.'s, and some in which the course of the illness is long term.

Cerebral embolism is either cardiac or non-cardiac in origin. Revelant cardiac conditions are those in which there may be intracavitary or mural thrombus or bacterial vegetations; therefore, it is not surprising that atrial fibrillation and other arrythmias head the differential list. Other conditions to be excluded are M.I. with mural thrombus formation, S.B.E., valvular heart disease, complications of surgery, etc. Some non-cardiac conditions of relevance are atherosclerosis of aortic arch, the carotids, or the cerebral vessels themselves, pulmonic vein thrombus, fat, tumour, and air embolus.

The exclusion of S.B.E. is particularly important, since this is a relatively common, treatable disease. The absence of splenomegaly and other relevant signs, including a normal white blood count and E.S.R., weighed against this.

The only possible causes of emboli that cannot be reasonably excluded in this patient are atherosclerosis of either aortic arch, carotids or cerebral vessels, and the chronic release of either atheromathous or mural thromboemboli of varying sizes. Stroke and cerebral infarction sometimes follow the non atheromatous, non thrombotic stenosis or occlusion of arteries and arterioles. This can occur as a result of disruption of the normal structure of vessel walls along parts of their length; also it has been suggested that stenosis can be due to vasospasm.[14] Particularly relevant here is the type of arterial and arteriolar wall disruption which is variously called hyalinosis, hypertensive fibrinoid arteritis, angionecrosis, etc. This type of change is similar to that seen in the kidney when there is sustained hypertension, but there is some suggestion that fibrinoid arteritis may often be confined to the brain alone.[15]

Zülch[16] cites evidence to the effect that there is no good correlation between arteriosclerosis in the cerebral circulation and that in the other areas of the body. He states categorically that chronic hypertension does not cause cerebral arteriosclerosis and there is no statistical basis for associating the two conditions. It is with reservation, therefore, that such a diagnosis is considered likely.

Hypertensive encephalopathy is a usually acute neurological disorder which develops in the presence of severe hypertension. Common symptoms are headache, seizures, transient episodes of impairment of consciousness to varying degrees, amaurosis, and focal signs such as hemiplegia, aphasia or hemianopia. Increased intracranial pressure causes palilloedema. Typically, a reduction in systemic arterial pressure to normotensive levels causes a disappearance of the signs and symptoms, but the high pressure is often refractory to treatment and causes death quickly.

The pathogenesis of the condition has been debated for many years and considerable physiological and pathological investigation has been carried out.

It has been suggested by Dinsdale et al that neuronal ischaemia, microinfarction and cerebral oedema follow the rapid elevation of the blood pressure to high levels, and that increased vascular reactivity and vasospasm

are responsible.[17] These workers believe that penetrating cerebral cortical arterioles may be chiefly involved, and that this may account for a rare pattern of multiple cerebral cortical microinfarction described by Rosenburg[18] in a post mortem study of a large series of hypertensives.

Byrom[19], who has studied this phenomenon for many years, using artificially hypertensive rats, has held that segmental vasoconstriction causes cerebral ischaemia and the consequent tissue damage. Skinhoj and Strandgaard[20] have recently examined the phenomenon of segmental vasoconstriction from the point of view that this represents normal physiologic compensation for elevated blood pressure (autoregulation) and that the intervening areas of dilatation show a pathologic failure of this mechanism. Using the xenon-133 technique, they determined the cerebral blood flow in 3 human subjects whose blood pressure was artificially raised with angiotensin, and determined that elevation past a certain point would cause a breakthrough in autoregulation and abnormally high brain perfusion. Factors other than blood pressure – notably high Pa CO_2 and low pH were implicated in this failure.

The authors tentatively conclude that the first stage in hypertensive encephalopathy is cerebral autoregulatory decompensation with hyperperfusion followed by brain oedema, and that the "breakthrough point" is significantly influenced by acid-base balance in the brain.

The presence of chronic livido reticularis and cyanosis of the distal parts of the digits is suggestive of the responsibility of a systemic vascular disease other than one which might be a consequence of hypertension, such as arteriosclerosis. The differential diagnosis of all the systemic and non-arteriosclerotic causes of cerebral infarction is comprehensively described by Aita[21], and it is not useful to reproduce that discussion here. Rather, it is more appropriate to briefly review some of the more common causes of peripheral vascular disease which have not already been excluded in another context above.

Livido reticularis is a chronic sign which does not correspond to any demonstrable microscopic abnormality, although local ischaemic ulcers sometimes show an acute vasculitis. Symptoms of coldness, numbness and paraesthesia are typical. The sign may appear as a result of a primary vascular disorder and is sometimes, as with this patient, associated with acrocyanosis. Raynaud's disease is a vasospastic condition which has a characteristic bilateral, symmetric distribution and temporal sequence of pallor, cyanosis, and erythema not observed in this case.

Thromboangiitis obliterans or Buerger's disease involves the entire neurovascular bundle – artery, vein and nerve, and there are signs of oedema, congestion and tenderness, as well as ischaemia. Peripheral pulses are often not palpable in the affected part. Clearly, these are not the observed peripheral signs.

In passing, it should be mentioned that there is considerable debate on the question of whether this disease exists as a separate nosological entity. Some authors recognize neither a cerebral nor a peripheral form of disease, and although there is a histological characterization of it, recent work suggests differing aetiologies. This condition, as it was thought to exist, has been associated in the past with diffuse cerebral cortical atrophy and dementia. Buerger's disease may be an entity which includes the consequences of recurrent thrombosis or embolism rather than a separately defined pathological process. Similarly, thromboangiitis obliterans of the brain bears no histological resemblance to Buerger's disease of the extremities and probably has multiple aetiologies.

Various hyperviscosity syndromes have been mentioned above. Cryoglobulinemia and macroglobulinemia might be thought of in this diagnosis, but the globulin studies in this patient were normal.

Finally, a generalized idiopathic, refractory increase of arteriolar tone could be responsible for the observed signs. This was excluded by a phentolamine blocking test that was normal; i.e. there was no disorder of neurochemical transmission at the nerve-vessel interface.

The clinical diagnosis can now be summarized. Since the differential process has been that of exclusion, the diagnoses are those entities which could not be ruled out, and in whose favour there is the greatest supporting evidence; the following are submitted:

1. Essential hypertension.
2. Secondary renal hypertension.
3. Hypertensive arteriolosclerosis.
4. Primary idiopathic peripheral arteriolar and small arterial occlusion.
5. Multiple cerebral infarctions, resulting in cortical atrophy and dementia.
6. Presenile dementia of the Alzheimer type.
7. Massive intracerebral hemorrhage.

PATHOLOGICAL FINDINGS

In general, the autopsy results correlate well with the clinical findings of hypertension and resulting target organ damage. There was generalized severe arteriolosclerosis, slight to moderate atherosclerosis of aorta and coronary arteries and, surprisingly, minimal left ventricular hypertrophy. The heart weighed 320 g. and the left ventricular wall was 1.7 cm. thick (1.5 cm. is considered the upper limit of normal). The relative lack of bulk and absence of overt morphological evidence of heart failure is enigmatic in a case of this sort, where there has been chronic pressure overload

over the course of many years. There was diffuse nephrosclerosis; the left and right kidneys weighed 90 and 100 g. respectively. The extent of this renal damage was consistent with long standing hypertension.

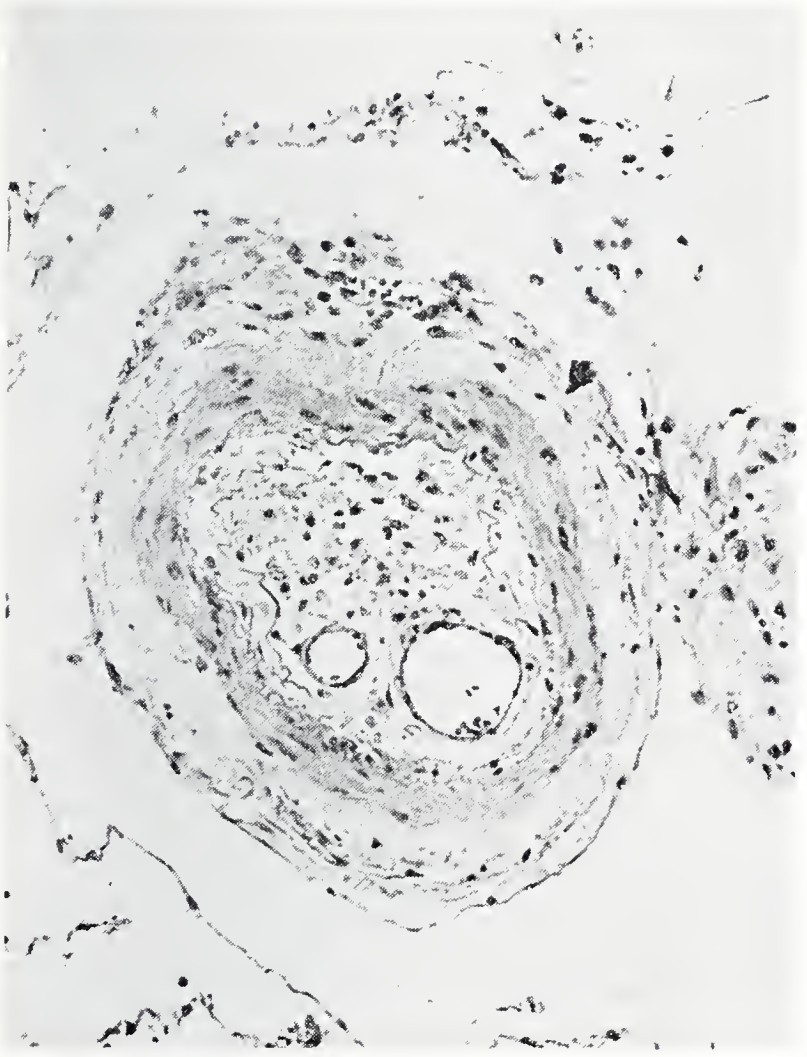


FIG. 1
A thrombosed and recanalized vessel overlying cerebral cortex. Note the disruption of the internal elastic lamina.

The cerebral vessels show a quite uncommon pattern of damage, in that it was so widespread and broad in distribution. There was severe, diffuse cerebral and cerebellar cortical ateriolosclerosis with hyperplasia of cerebral cortical arterial walls, organized, recanalized thrombosis of multiple cerebral cortical arteries, and mild retinal arteriolosclerosis. These vascular lesions are of varying ages, some very old and some relatively new (see Figures 1 and 2), indicating an ongoing, chronic process.

The brain parenchyma showed multiple small infarctions of varying ages (see Figure 3) in the cerebral and cerebellar cortices. These were responsible for a gross appearance of granular cortical atrophy (Figure 4). There were multiple, old, minute hemorrhages deep in the cerebral hemispheres, a not uncommon finding in cases of long standing hypertension.

Findings of primary C.N.S. degeneration were conspicuously absent. There were no senile plaques, neurofibrillary tangles, or areas of demyelination, and the basal ganglia were normal. Thus, Alzheimer's disease and other postulated disorders can be excluded. Also absent was any evidence of a source of emboli which might have been the cause of repeated strokes. All the major vessels were patent and no mural thrombus, bacterial vegetation, atrial myxoma or other embolic source could be demonstrated in the heart.

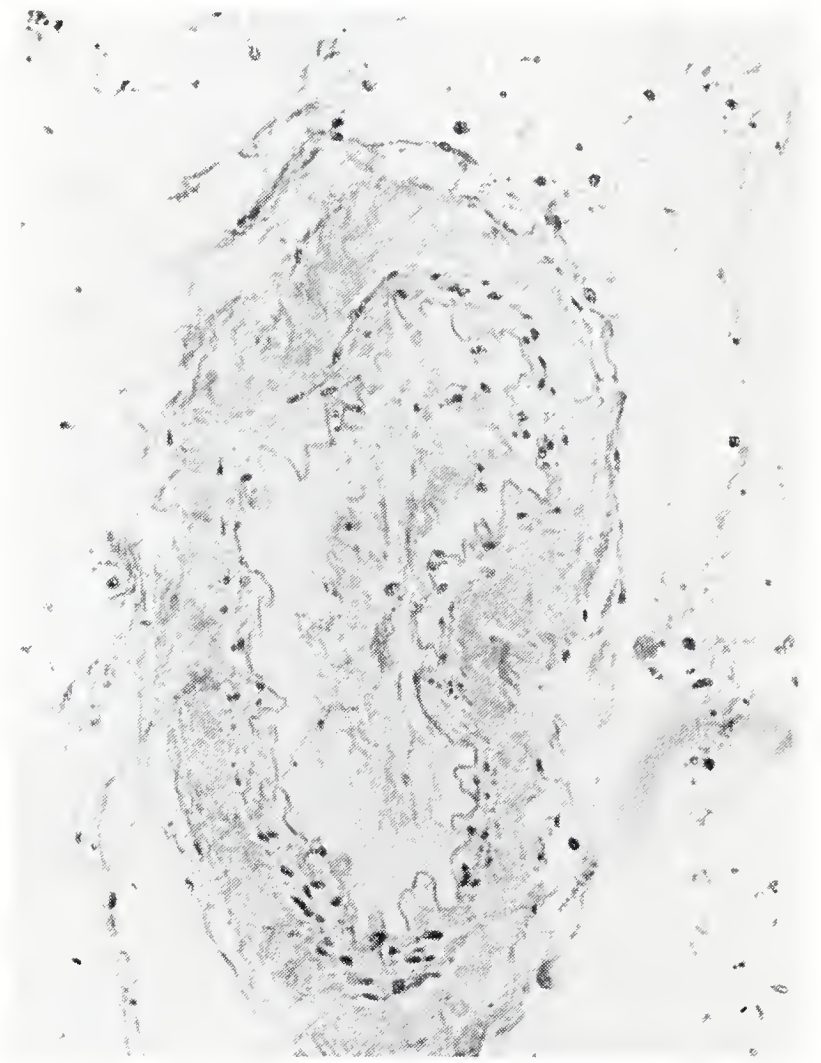


FIG. 2
An occluded vessel, as in Fig. 1, except older. Note the increasing structural disorganization and the filling of the lumen with fibrous material.

The immediate cause of death was a massive intracerebral hemorrhage into the right parietooccipital area. There was intraventricular extension (lateral, III and IV ventricles) and, also hemorrhage into the cranial and spinal subarachnoid spaces. This bleeding undoubtedly caused the terminal clinical signs of weakness, paralysis and mental deterioration. There were herniations of hippocampal unci and cerebellar tonsils and flattening of the gyri, further evidence of acutely increasing intracranial pressure, and it is most likely that this terminal sequence was, like the chronic neurological decline, due to hypertension.

In summary, the pathological examination revealed widespread evidence of hypertensive target organ damage. There were diffuse arteriolosclerosis, mild to moderate atheromatous changes in the aorta and coronaries, multiple occlusions of cerebral and cerebellar cortical vessels, resulting in multiple old and new infarctions and, as the cause of death, a typical massive hypertensive intracerebral hemorrhage.

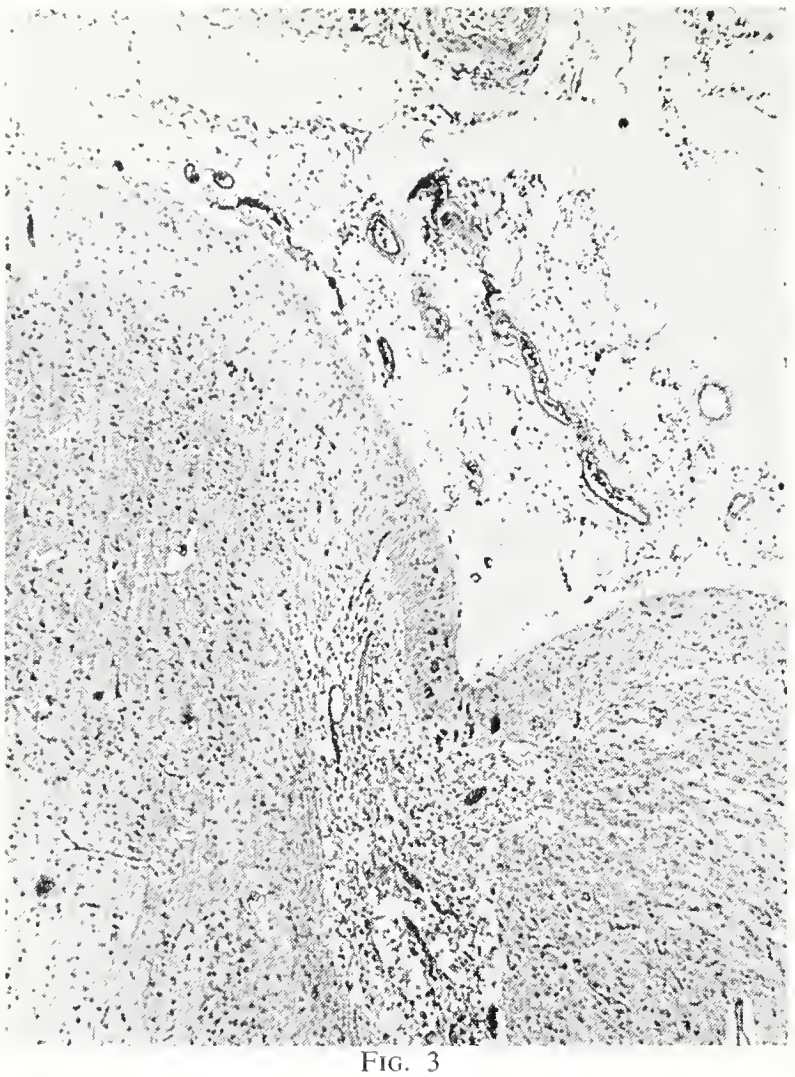


FIG. 3
The cerebral cortex, showing an infarct of some duration. Note the typical preservation of the molecular layer.

FIG. 4
The surface of the brain shows typical granular cortical atrophy.

A question which presents itself at this point is whether or not some recognized disease entity exists which includes all of the features of this case.

On clinical grounds one might think of a condition first described by Binswanger in 1894 – "progressive subcortical encephalopathy". The onset is classically in the fifth or sixth decade, but can be earlier, with progressing memory loss, punctuated by seizures and focal incidents. Pseudobulbar palsy and dementia are late findings, occurring terminally, and there is a frequent association with hypertension. However, granular cortical atrophy is not seen in this condition, which is a form of cerebral arteriosclerosis affecting the perforating vessels of the white matter and the subcortical gray substance.[22] The vascular changes lead to "multiple small areas of subcortical infarction with diffuse areas of slight demyelination secondary to interruption of long tracts".[23]

Binswanger's original publication is incomplete with respect to details of the pathology of this condition, but it is generally accepted that unexplained cases of subcortical demyelination, not definitely associated with arteriosclerosis, ought not to be associated with the eponym "Binswanger's Disease". Some recent work by Okeda[24] using linear regression analysis in a morphometric comparison of the vascular damage of clinically diagnosed Binswanger's disease and that of hypertensive encephalopathy has suggested that there may be some pathogenetic similarly between the two conditions; however, there has been no physiologic demonstration or confirmation of the role of vasospasm or the breakdown of autoregulation in the causation of an intracerebral "steal" from the affected areas.

Cerebral amyloidosis has been known to cause the type of atrophy and multiple small infarcts seen in this case, but there is no morphological evidence of amyloid deposition in the cerebral vessels or elsewhere. This condition is associated with a later age of onset than that in this case, and is usually found in association with senile plaques in the cerebral cortex.

Recalling the above mentioned anatomic and hemodynamic factors in the pathogenesis of cerebral infarction, it is useful to review Pentschew's discussion[25] of cardiac and circulatory collapse encephalopathy. He showed that cardiac failure, with intermittent episodes of hypotension, was associated with granular atrophy in hypertensives. The cases he observed all had the atrophy in a characteristic sickle shaped distribution across the hemispheric convexity. This distribution corresponded to the border zones of supply of the great circumferential arteries. Other workers observed an obliterative vasculitis of similarly affected vessels and there was considerable controversy as to the relative influence of systemic and local circulatory factors.

Wildi[26] postulated that the observed granular atrophy and obliterative endangiitis both result from repeated

episodes of cardiac insufficiency in hypertensives but, although concomitant, are independent happenings. The repeated episodes of oligaemia supposedly stimulate the proliferation of subendothelial connective tissue in the penetrating vessels of the border zones and, subsequently, occlusion.

This hypothesis has been challenged on the grounds that while oligaemic episodes are common in hypertensives, granular atrophy is quite rare. In reply to this, Pentschew holds that the selective vulnerability of the border zones is individually determined.[27] In addition, he points out that the border zone concept is valid for the basal ganglia and cerebellar cortex and that the pattern of distribution of the lesions is subject to variations as diverse as those of the anastomotic circulations of individual subjects.

The applicability of this concept to the case at hand seems considerable, but there are several factors which must remain as open questions. The clinical evidence for episodes of cerebral hypotension is not definite. There is no denying that some or even many of the recorded strokes could have been due to hypotensive oligaemia, but they could as well have been due to embolism or thrombosis, as most current opinion would hold.

To briefly review and summarize this case, we are presented with a young adult who becomes hypertensive and demented over a long period. Essential hypertension probably was the initial lesion. With time renal hypertension developed, as did marked cerebral atrophy. There was no heart failure or cardiac insufficiency, and extensive investigations over the course of six years could not account for the dementia or demonstrate any medical disease other than renal hypertension. The main gross and microscopic autopsy findings were all explicable as sequelae of hypertension and there was no structural evidence of any other underlying disease.

Pathological Diagnoses

1. Generalized arteriolosclerosis.
2. Nephrosclerosis.
3. Severe diffuse cerebral and cerebellar cortical arteriolosclerosis.
4. Multiple cerebral cortical arterial thromboses, many with organization and recanalization.
5. Multiple small infarctions of cerebral and cerebellar cortex.
6. Patchy, marked granular atrophy of cerebral and cerebellar cortices.
7. Terminal massive intracerebral hemorrhage with intraventricular and subarachnoid extension.

For the Diagnostic Approach to Hypertension see:

1. Paine, R. and Sherman, W. in *Signs and Symptoms* (ed. by MacBryde, C. and Blacklow, R.), pp. 272-291. Philadelphia, 1970.
2. Laragh, J. in *Textbook of Endocrinology* (ed. by Williams R. H.). pp. 948-950. Philadelphia, 1974.

NOTES

1. Adams, R. and Victor, M. in Harrison's *Principles of Internal Medicine* (ed. by Wintrobe et al), p. 194. New York, 1970.
2. Ibid, p. 195.
3. Hachinski, V. et al, *Lancet*, 207-210, July 17, 1974.
4. Fisher, C. M. et al in Harrison's *Principles of Internal Medicine*, pp. 1728-1729.
5. Zulch, K. in *Pathology of the Nervous System* (ed. by Minckler, J.), 2: 1510. New York, 1971.
6. Carter, A. B. in *Handbook of Clinical Neurology* (ed. by Vincken, P. and Bruyn), 11: 301, Amsterdam, 1972.
7. Fisher, C. M., *Neurology*, 15: 774-785, 1965.
8. Ibid, p. 783.
9. Carter, p. 303.
10. Fisher, C. M. et al, p. 1729.
11. Torvik, A. et al. *Acta Neurol. Scand.*, 47: 137-150, 1971.
12. McDowell, F. in *Handbook of Clinical Neurology*, p. 404.
13. Fisher, C. M. and Pearlman, A., *Neurology*, 17: 1025-1032, 1967.
14. Dinsdale, H. et al, *Europ. Neurol.*, 6: 29-33, 1971/72.
15. Ziegler, D. K. in *Handbook of Clinical Neurology*, p. 561.
16. Zulch, p. 1518.
17. Dinsdale et al, pp. 29-33.
18. Rosenburg. E. *Arch. Int. Med.*, 64, p. 545, 1940.
19. Byrom, F. *The Hypertensive Vascular Crisis*. New York, 1969.
20. Skinhoj, E. and Strandgaard, S. *Lancet*. I, p. 461, 1973.
21. Aita, J. in *Handbook of Clinical Neurology*, p. 421.
22. Olszewski, J. *World Neurology*, 3, p. 373, 1962.
23. Ibid., p. 373.
24. Okeda, R. *Neurol. Inst., Univ. Wien – Acta Neuropath. (Berl.)*, 26/1, 23-43, 1973.
25. Pentschew, A. in *Pathology of the Nervous System*, pp. 1626-1627.
26. Wildi, E. *Bull. Acad. Suisse Sci. Med.*, 15 (Fase 1), 18, 1959.
27. Pentschew, A., p. 1627.

ACKNOWLEDGEMENT

The author acknowledges with thanks the assistance and counsel of Dr. N. B. Rewcastle, Professor of Neuropathology in the Department of Pathology, who supplied the case material and photographs, as well as a considerable amount of time in discussion of many of the points raised above.

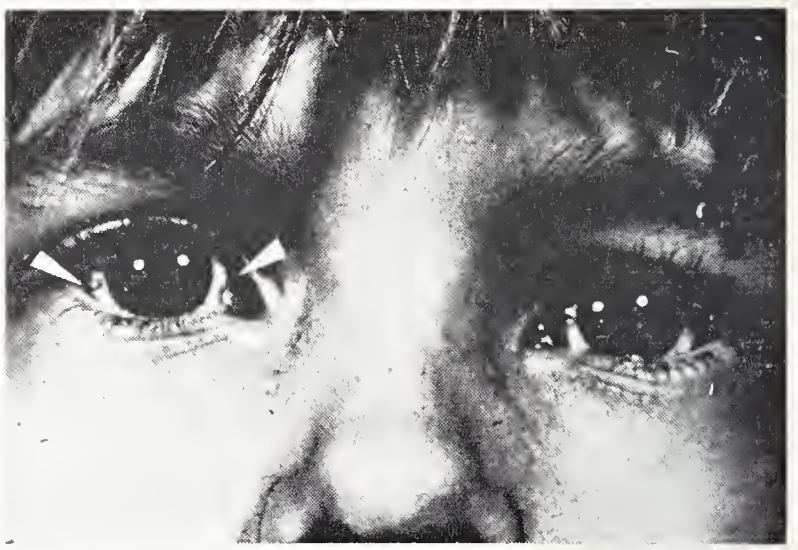
INDEX TO ADVERTISERS

THE CANADIAN ARMED FORCES	48
CANADIAN PREMIER LIFE INSURANCE	64
CANADA LIFE ASSURANCE	65
PRINCESS MARGARET HOSPITAL	Inside back cover
SASKATOON COMMUNITY CLINIC	Inside back cover
MEDICAL ALUMNI ASSOCIATION	Outside back cover

Grand Round Quiz — Questions

William Halliday 7T5

This child, who has always had trouble walking, walks with a broad base. A review of the past medical history would probably show the occurrence of frequent sinopulmonary infections.

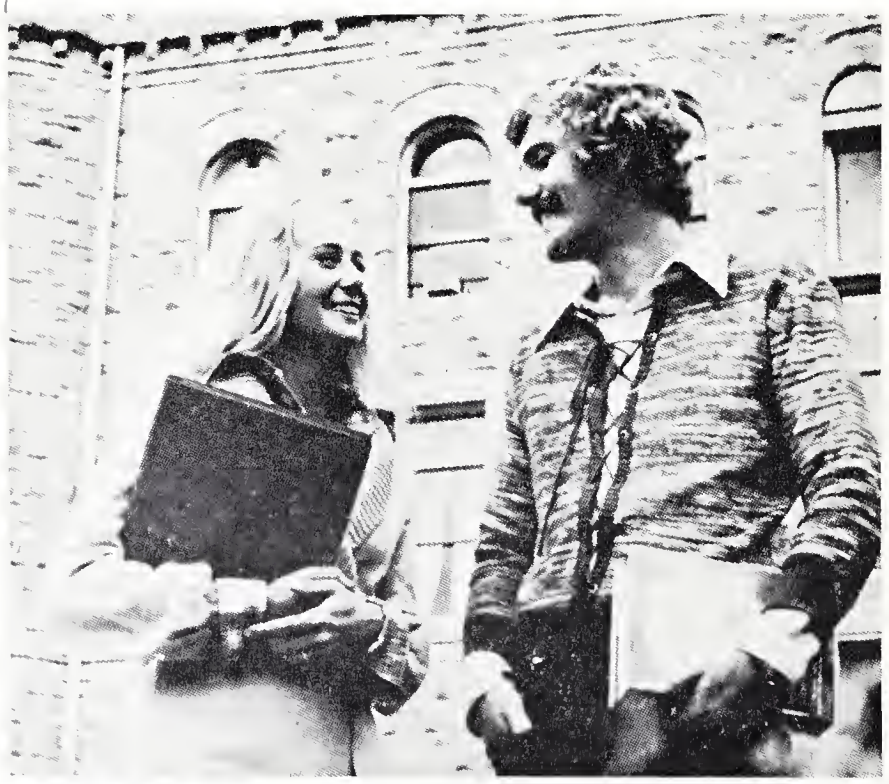


QUESTION

1. *What are the lesions shown in the above photographs?*
2. *In what group of syndromes is this disease included?*
3. *What syndrome or disease does this child have?*

ERRATUM: Vol. LII, Number 2, Dec. 1974, **Ophthalmology** Line 21, page 25 should read: "Characteristic of the supranuclear palsy is the **in**ability to move both eyes in a given direction, the absence of any strabismus when the eyes are observed, and the absence of any diplopia."

Student life insurance...do you need it?



Right now, you're probably finding it hard to make ends meet. It costs money to go to school, and you have some pretty large obligations, especially if you have a young family. What if a disaster should occur? How would they manage? The Doctor's Life Plan by Canadian Premier Life Insurance Company could make the burden a little easier to bear. It will help you and your family plan for a financially secure future. Costs so little. Assures so much. And when the time comes for you to change your Doctor's Life Plan to permanent life insurance, we have a full range of plans. Medical check-ups are seldom required. *Doctor's Life Plan! – Think about it!* – You just might need it! *Call your representative now!*

Four branches to serve you:

Toronto Metro: 715-2 Carlton Street
Phone: 366-5649 – Tony Martin, *Manager*

Toronto Centre: 101-201 Consumers Road
Phone: 493-4160 – E. Red Finn, *Manager*

Toronto Simcoe: 304-365 Evans Avenue
Phone:255-5513 – Louis J. D'Alton, *Manager*

Toronto King: 714-2 Carlton Street
Phone: 363-1468 – Jeffrey J. Jennings, *Manager*

CANADIAN PREMIER LIFE INSURANCE COMPANY

STUDENT LIFE INSURANCE SPECIALISTS

Book Review

TEXTBOOK OF CHILD NEUROLOGY

John H. Menkes, M.D. Lea and Febiger, 1974
Philadelphia, pp 583. Canadian List Price $24.50
Reviewed by Keith L. Meloff, M.D., F.R.C.P.(C)
Pediatric Neurologist, Hospital for Sick Children
Assistant Professor of Pediatrics, University of Toronto.

I am often asked to recommend suitable textbook material in Pediatrics, Neurology, Neurosurgery and Pediatric Neurology. These requests come from medical students, interns, residents and colleagues in different disciplines.

I recommend the following without hesitation:

1. *Neurology* – the sections in Harrison's "Principles of Internal Medicine"
2. *Pediatrics* – the textbook by Barnett which has a superb introduction to Pediatric Neurology.
3. *Pediatric Neurology* – the recently published text by Menkes which is the subject of this review.

Other books, notably those by Ford, Farmer, Bray, Lagos, Gamstorp and Swaiman and Wright are available and have their peculiar strengths and weaknesses. The section in Farmer on the neurologic exam is excellent. Menkes' book does not have such a section but refers to the definitive book by Paine and Oppe. Ford's text is of historical interest. Bray, Lagos and Gamstorp are a bit superficial and not too well organized. Swaiman and Wright's book stresses neuromuscular disorders, a weakness in Menkes' book.

Overall, however, Menkes has done an admirable job and has performed a valuable service to students of child neurology at all levels of sophistication.

The book is organized into 13 chapters including sections on metabolic and genetic diseases, malformations, infections, toxic disorders, tumors, paroxysmal disorders, neuromuscular diseases and disorders of mental development.

The first two chapters on metabolic and heredodegenerative diseases are, as one would expect, superb. Menkes has made major contributions to this field. (For example, he was the first to describe Maple Syrup Urine Disease, an inborn error of metabolism which has improved our understanding of the chemistry of branched chain amino acids. The disorder of copper metabolism, Kinky Hair Disease, was also first described by Menkes).

Dr. Ronald Gabriel has contributed a masterful chapter on Central Nervous System malformations. Lucid and succinct, it is essential reading for all concerned about this important area.

The chapter on Infections of the Nervous System by Dr. Marvin Weil, is equally impressive. Dr. Weil is an authority in this area and has covered this broad field in a scholarly and clinically useful way.

Dr. Marcel Kinsbourne gives us a glimpse of his immense talents in the chapter on Disorders of Mental Development. His chapter is, regrettably, too short and does not appropriately reflect the important health problems that physicians will see in their practice.

Now for the bad news: Schilder's Disease should not be considered in a chapter on autoimmune and postinfectious disease since there is no evidence for an immunological basis to this disease. Vertiginous disorders should be included in the chapter on Paroxysmal Disorders. The chapter on diseases of the motor unit does not contain the same profound, basic scientific approach that the chapters on metabolic and degenerative diseases do.

These are minor criticisms and do not detract from the overall value of the book. It reads well and has an excellent and remarkably recent bibliography. It is well indexed, and not least important, the price is right. Menkes' "Textbook of Child Neurology" deserves a place in every student's library.

Professional Planning
for Professionals

Douglas Wiley

Send for your free copy of
"A Doctor Looks at Life Insurance"

340 University Avenue
Toronto M5G 1R8
595-1400

THE CANADA LIFE ASSURANCE COMPANY

Grand Round Quiz — Answers

1. *The photos show telangiectasia on a) the ear and b) the bulbar conjunctiva.*

2. *This syndrome belongs to the group of diseases known as the neurocutaneous syndromes. Magalini, in his book, Directory of Medical Syndromes, lists the following as neurocutaneous syndromes:*

    1) Bourneville's syndrome
    2) Cataracta dermatogenes syndrome
    3) Linear nevus sebaceus-convulsions-mental retardation syndrome
    4) Louis-Barr syndrome (ataxia-telangiectasia)
    5) Neurocutaneous melanosis syndrome
    6) Sturge-Weber syndrome
    7) von Hippel-Lindau syndrome
    8) von Recklinghausen syndrome

3. *This child has ataxia-telangiectasia.*

    (Synonyms: Boder-Sedgwick syndrome, Louis-Barr syndrome and Cephalo-oculocutaneous telangiectasia)

DISCUSSION

Ataxia-telangiectasia (A-T) is a chronic progressive disorder which was once thought to affect primarily the nervous system. However, as a result of improved investigative methodology and the fact that affected patients are living longer, it has become apparent that A-T is an autosomal recessive, multi-system disease. The ataxia begins when the child starts to walk; later, generally around five years of age, the telangiectasia appears on the bulbar conjunctiva. Other areas that may develop telangiectasia are the ears, the nose and cheeks (on which it appears in a butterfly distribution), the palate, sternum, antecubital and popliteal fossae and the dorsum of the extremities.

These children exhibit growth retardation and, during the course of the disease, may develop chorcoathetoid movements, myoclonic movements, intention tremors, dysarthria, drooling and a fixation nystagmus. Children with A-T have an increased incidence of neoplasms and sino-pulmonary infections. Repeated chest infections can render the child a pulmonary cripple and are frequently the cause of death.

In addition to the aforementioned neurological findings, it is found that patients who have had A-T for ten to fifteen years may develop peripheral weakness accompanied by muscle wasting and may lose the appreciation of vibration and position. Investigations into the haemotologic, hepatic, endocrine, ovarian, testicular, skeletal muscle and peripheral nerve functions are revealing an array of abnormalities.

Many of these children are found to be immunologically deficient in one or both of the humoral and cellular immune systems. Analysis of the humoral system may reveal a low or absent IgA, a low or absent IgE, a slightly reduced IgG and the presence of low molecular weight IgM. Thymic maldevelopment is recognized as an integral part of A-T. Evaluation of the cellular immunity may reveal a lymphocytopenia and poor or absent responses to common skin test antigens. These immunological findings may explain the increased incidence of neoplasms and sino-pulmonary infections in children with A-T.

In summary, it is best to think of A-T as a multi-system disease. Each patient is an individual and may have many or few of the above findings. Classically, all children with A-T are ataxic and have telangiectasia.

BIBLIOGRAPHY

1. Magalini, Dr. S., *Dictionary of Medical Syndromes*. J. B. Lippincott Co., Philadelphia and Toronto, 1971.
2. Korein, J., Steinman, P. A. and Senz, E. H. *AMA Ach. Neurol.* 4: 272, 1961.
3. Sedgwick, R. P. and Boder, E. *Neurol.*, 10: 705, 1960.
4. McFarlin, D. E., Strober, W. and Waldmann, T. A. *Medicine*, 51: 281-314, 1972.

(cont'd from page 53)

primarily by raising brain 5-HT comes from this evidence.

The problems in research of brain biochemistry are exceedingly complex ones, but great strides have recently been made. Although correlation of biochemical events and brain function, including behaviour, is next to impossible, the implications are far-reaching. It will be interesting to follow the role of serotonin in this regard.

ACKNOWLEDGEMENT

I wish to thank Dr. D. L. Bloxam, Dept. of Pathology, for his encouragement and assistance in editing this article.

REFERENCES

1. Curzon, G., Joseph, M. H., and Knott, P. J. (1972). "Effects of immobilization and food deprivation on rat brain tryptophan metabolism." J. Neurochem. *19*, 1967.
2. Curzon, G. (1971), "Effects of stress and adrenal harmones on brain serotonin." Am. J. Clin. Nutrition *24*, 830.
3. Coppen, A., Eccleston, E. G. and Pret, M. (14th July, 1973), "Total and free tryptophan concentration in the plasma of depressive patients." Lancet *II*, 60.
4. Grahame-Smith, D. G. (1971), "Studies *in vivo* on the relationship between brain tryptophan, brain 5-HT synthesis, and hyperactivity in rats treated with MAOI and L-tryptophan." J. Neurochem. *18*, 1053
5. Williams, T. A., Katz, M., and Shield, J. (editors), *Recent advances in phychobiology and depressive illness*. U.S. Government Printing Office, 1972.
6. Lovett-Doust, J. W., and Huszka, L. (1972), "Amines and aphrodisiacs in chronic schizophrenia." J. Nerv. and Ment. Dis. *155*, 261.
7. Barchas, J., and Usdin, E., *Serotonin and behaviour*. Academic Press, 1973.

CANADA
THE PRINCESS MARGARET HOSPITAL

RESIDENT TRAINING IN THERAPEUTIC RADIOLOGY

The Ontario Cancer Institute incorporating The Princess Margaret Hospital offers a three year programme which combines clinical work on the wards and in the Out-patient Department of the hospital, and didactic courses in Anatomy, Nuclear Medicine, Tumour Pathology, Physics, Radiobiology, and Radiation Therapy. This course leads to the Diploma in Medical Radiology (Therapeutic) from the University of Toronto, and is accredited by the Faculty of Radiologists in London. The hospital is recognized by The Royal College of Physicians and Surgeons of Canada, and the American Board of Radiology, for complete training in Radiotherapy over a period of three years. In addition it is accredited for Internal Medicine and Anatomic Pathology for a period of one year, and for six months in Diagnostic Radiology.

The Princess Margaret Hospital provides complete facilities for cancer research, diagnosis and treatment, exclusive of major surgery. Over 4,800 new patients are seen annually; there are 175 active treatment beds, and facilities include six Cobalt Units, two Caesium Units, a Betatron, and a 35 Mv Linear Accelerator. Salaries range from $12,750 to $15,750 per annum. Applications are now accepted for July 1976, and must be completed by 30th September, 1975.

For further information, write to:

Director of Medical Education
THE PRINCESS MARGARET HOSPITAL
500 Sherbourne Street
Toronto, Ontario, Canada M4X 1K9

THE PRINCESS MARGARET HOSPITAL

TRAINING IN CLINICAL ONCOLOGY

The Ontario Cancer Institute incorporating The Princess Margaret Hospital offers resident training in Oncology (both radiotherapy and chemotherapy), thus providing clinical experience and didactic teaching of the non-surgical methods of managing cancer patients. The first year of training will be identical for all trainees, including clinical and didactic training in both Radiation Oncology and Medical Oncology (chemotherapy, hormone therapy, immunotherapy, etc.). The second and third years will be devoted to either Radiation Oncology or Medical Oncology, with some exposure to Paediatric Oncology.

Preference is given to applicants with two years of training in Internal Medicine or Paediatric Medicine, but serious consideration will be given to Radiation Oncology applicants with only one year of resident training in either, or with training in Surgery or Obstetrics and Gynaecology. Salaries range from $12,750 to $15,750 per year.

The Princess Margaret Hospital provides complete facilities for cancer research, diagnosis and treatment, exclusive of major surgery. Over 4,800 new patients are seen annually; there are 175 active treatment beds. Applications for July, 1976, must be completed by 30th September, 1975.

For further details write to:

Director of Medical Education
THE PRINCESS MARGARET HOSPITAL
500 Sherbourne Street
Toronto, Ontario, Canada M4X 1K9

COMMUNITY CLINIC

455 SECOND AVENUE NORTH
SASKATOON, SASKACHEWAN
S7K 2C2
TELEPHONE 652-0300

ADMINISTRATOR
C. A. Robson

We are recruiting family physicians for 1974, 1975, 1976.

The Community Health Services (Saskatoon) Association, through the Community Clinic is providing truly innovative and exciting ways of delivering health services.

We are urgently in need of physicians due to the expanding out-reach programs.

If you want an interesting and stimulating opportunity to practise medicine in a team environment, contact the Medical Co-ordinator at the Community Clinic.

University of Toronto
Library, Serials Dept.
Toronto, Ontario
M5S 1A5

MEDICAL ALUMNI ASSOCIATION

UNIVERSITY OF TORONTO

Room 10, 280 Bloor St. W., Toronto, Canada M5S 1W1

Telephone 928-2695 Area Code 416

The Student Aid Committee of the University of Toronto Medical Alumni Associc has a budget of $35,000 for 1974-75. This money is to be spent as follows:–

Scholarships ..... (4 scholarships of $250 have been awarded; 3 scholarships of $250 and a graduation scholarship of $500 are to be awarded.	$ 2,250.00
Undergraduate bursaries ..... (This bursary money is awarded by the Faculty Sub-Committee on Awards)	4,000.00
Transportation fund for Medical student electives ..... (The maximum individual grant is $150. Applications for 1975-76 electives are being accepted up to April 15, 1975 for the period June 2, 1975 - November 16, 1975, and up to October 1, 1975 for the period November17, 1975 to May 2, 1976)	6,000.00
Medical Student Summer Fellowships ..... (15 Fellowships at $1,200. 8 of these are for Family Practice)	18,000.00
Graduate bursaries	1,000.00
Fund for Educational Activities	500.00
Not yet assigned	3,250.00

The Student Aid Committee administers two special funds. The **Dr. Bernard A. Manace Award** (value $80) provides assistance to a Medical student from any year who is undertaking an elective or summer Medical experience in Israel. Preference is given to a student working in the area of Immunology or Allergy. Consideration is given to academic standing. The **Dr. L. Nelles Silverthorne Award** (value $140) provides assistance to a Medical student from any year who is undertaking an elective or summer Medical experience in a remote area. Preference is given to a student working in a mission hospital. Consideration is given to financial need. The deadline for applications for these two awards is March 1, 1975 for the subsequent twelve month period.

The Student Aid Committee also has responsibility for three loan funds. **The Medical Alumni Association Undergraduate Loan Fund** – The main purpose of this fund is to provide short term, interest free loans to Medical students who require financial assistance during periods of temporary difficulty. **The Robert Elgin Towle Loan Fund** – This is an endowed loan fund which can provide interest free loan assistance to female undergraduates. **The Medical Alumni Association Graduate Loan Fund (including the Emma Bissell and Agnes E. Hamshaw Funds)** – The purpose of this fund is to provide interest free loans of up to $1,500 per year to physicians taking postgraduate training.

Further information about any of the above, and application forms where required, can be obtained from Mrs. N. S. Shenstone, Secretary, Medical Alumni Association.